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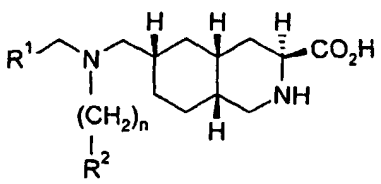

I

(57) Abstract: The present invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, pharmaceutical compositions comprising an effective amount of a compound of Formula I in combination with a suitable carrier, diluent, or excipient, and methods for treating neurological disorders and neurodegenerative diseases comprising administering to a patient in need thereof an effective amount of a compound of Formula I.

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ISOQUINOLINE-3-CARBOXYLIC ACID DERIVATIVES AS EXCITATORY AMINO ACID RECEPTOR ANTAGONISTS

In the mammalian central nervous system (CNS), the transmission of nerve impulses is controlled by the interaction between a neurotransmitter, that is released by a sending neuron, and a surface receptor on a receiving neuron, which causes excitation of this receiving neuron. L-Glutamate, which is the most abundant neurotransmitter in the CNS, mediates the major excitatory pathways in mammals, and is referred to as an excitatory amino acid (EAA). The receptors that respond to glutamate are called excitatory amino acid receptors (EAA receptors). See Watkins & Evans, Ann. Rev. Pharmacol. Toxicol., 21, 165 (1981); Monaghan, Bridges, and Cotman, Ann. Rev. Pharmacol. Toxicol., 29, 365 (1989); Watkins, Krogsgaard-Larsen, and Honore, Trans. Pharm. Sci., 11, 25 (1990). The excitatory amino acids are of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiration, cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types. Receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic." This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainic acid (KA). Molecular biological studies have established that AMPA receptors are composed of subunits (GluR1 – GluR4), which can assemble to form functional ion channels. Five kainate receptors have been identified which are classified as either High Affinity (KA1 and KA2) or Low Affinity (composed of GluR5, GluR6, and/or GluR7 subunits). Bleakman et al., Molecular Pharmacology, 49, No.4, 581,(1996).

The second general type of receptor is the G-protein coupled or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis,

activation of phospholipase D, increases or decreases in cAMP formation, and changes in ion channel function. Schoepp and Conn, Trends in Pharmacol. Sci., 14, 13 (1993).

Both types of excitatory amino acid receptor appear not only to mediate normal synaptic transmission along excitatory pathways, but also to participate in the modification of synaptic connections during development and throughout life. Schoepp, Bockaert, and Sladeczek, Trends in Pharmacol. Sci., 11, 508 (1990); McDonald and Johnson, Brain Research Reviews, 15, 41 (1990).

The excessive or inappropriate stimulation of excitatory amino acid receptors leads to neuronal cell damage or loss by way of a mechanism known as excitotoxicity. This process has been suggested to mediate neuronal degeneration in a variety of neurological disorders and conditions. The medical consequences of such neuronal degeneration makes the abatement of these degenerative neurological processes an important therapeutic goal. For instance, excitatory amino acid receptor excitotoxicity has been implicated in the pathophysiology of numerous neurological disorders, including the etiology of cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord lesions resulting from trauma or inflammation, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage. In addition, excitotoxicity has been implicated in chronic neurodegenerative conditions including Alzheimer's Disease, Huntington's Chorea, inherited ataxias, AIDS-induced dementia, amyotrophic lateral sclerosis, idiopathic and drug-induced Parkinson's Disease, as well as ocular damage and retinopathy. Other neurological disorders implicated with excitotoxicity and/or glutamate dysfunction include muscular spasticity including tremors, drug tolerance and withdrawal, brain edema, convulsive disorders including epilepsy, depression, anxiety and anxiety related disorders such as post-traumatic stress syndrome, tardive dyskinesia, and psychosis related to depression, schizophrenia, bipolar disorder, mania, and drug intoxication or addiction (see generally United States Patent No. 5,446,051 and 5,670,516). In addition, published International Patent application WO 98/45720 reports that excitatory amino acid receptor excitotoxicity participates in the etiology of acute and chronic pain states including severe pain, intractable pain, neuropathic pain, post-traumatic pain.

It is also known that trigeminal ganglia, and their associated nerve pathways, are associated with painful sensations of the head and face such as headache and, in particular, migraine. Moskowitz (Cephalalgia, 12, 5-7, (1992) proposed that unknown triggers stimulate the trigeminal ganglia which in turn innervate vasculature within cephalic tissue, giving rise to the release of vasoactive neuropeptides from axons innervating the vasculature. These neuropeptides initiate a series of events leading to neurogenic inflammation of the meninges, a consequence of which is pain. This neurogenic inflammation is blocked by sumatriptan at doses similar to those required to treat acute migraine in humans. However, such doses of sumatriptan are associated with contraindications as a result of sumatriptan's attendant vasoconstrictive properties.(see MacIntyre, P.D., et al., British Journal of Clinical Pharmacology, 34, 541-546 (1992); Chester, A.H., et al., Cardiovascular Research, 24, 932-937 (1990); Conner, H.E., et al., European Journal of Pharmacology, 161, 91-94 (1990)). Recently, it has been reported that all five members of the kainate subtype of ionotropic glutamate receptors are expressed on rat trigeminal ganglion neurons, and in particular, high levels of GluR5 and KA2 have been observed. (Sahara et al., The Journal of Neuroscience, 17(17), 6611 (1997)). As such, migraine presents yet another neurological disorder which may be implicated with glutamate receptor excitotoxicity.

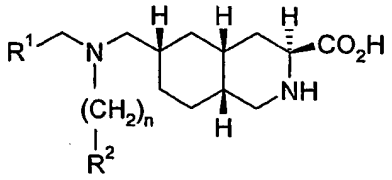
The use of a neuroprotective agent, such as an excitatory amino acid receptor antagonist, is believed to be useful in treating or preventing all of the aforementioned disorders and/or reducing the amount of neurological damage associated with these disorders. For example, studies have shown that AMPA receptor antagonists are neuroprotective in focal and global ischemia models. The competitive AMPA receptor antagonist NBQX (2,3-dihydroxy-6-nitro-7-sulfamoylbenzo[f]quinoxaline) has been reported effective in preventing global and focal ischemic damage. Sheardown et al., Science, 247, 571 (1900); Buchan et al., Neuroreport, 2, 473 (1991); LePeillet et al., Brain Research, 571, 115 (1992). The noncompetitive AMPA receptor antagonists GKYI 52466 has been shown to be an effective neuroprotective agent in rat global ischemia models. LaPeillet et al., Brain Research, 571, 115 (1992). European Patent Application Publication No. 590789A1 and United States Patents No. 5,446,051 and 5,670,516

disclose that certain decahydroisoquinoline derivative compounds are AMPA receptor antagonists and, as such, are useful in the treatment of a multitude of disorders conditions, including pain and migraine headache. WO 98/45270 discloses that certain decahydroisoquinoline derivative compounds are selective antagonists of the iGluR5 receptor and are useful for the treatment of various types of pain, including; severe, chronic, intractable, and neuropathic pain. Thus,excitatory amino acid receptor antagonists may also be useful as analgesic agents and for treating or preventing various forms of headache, including cluster headache, tension-type headache, and chronic daily headache.

In accordance with the present invention, Applicants have discovered novel compounds that are antagonists of the iGluR5 receptor subtype and, thus, could be useful in treating the multitude of neurological disorders or neurodegenerative diseases, as discussed above. Such antagonists could address a long felt need for safe and effective treatments for neurological disorders, without attending side effects. The treatment of neurological disorders and neurodegenerative diseases is hereby furthered.

SUMMARY OF THE INVENTION

The present invention provides a compound of Formula I



I

wherein:

R^1 is 3-hydroxyisoxazol-5-yl or tetrazol-5-yl;

R^2 is aryl, substituted aryl, (3-10C)cycloalkyl, heterocycle, or substituted heterocycle; and

n is 1 or 2;

or a pharmaceutically acceptable salt or prodrug thereof.

In addition, the present invention provides a method of treating or preventing a neurological disorder, or neurodegenerative condition, comprising administering to a patient in need thereof an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof. Examples of such neurological disorders, or neurodegenerative conditions, include: cerebral deficits subsequent to cardiac bypass surgery and grafting; stroke; cerebral ischemia; spinal cord lesions resulting from trauma or inflammation; perinatal hypoxia; cardiac arrest; hypoglycemic neuronal damage; Alzheimer's Disease; Huntington's Chorea; inherited ataxias; AIDS-induced dementia; amyotrophic lateral sclerosis; idiopathic and drug-induced Parkinson's Disease; ocular damage and retinopathy; muscular spasticity including tremors; drug tolerance and withdrawal; brain edema; convulsive disorders including epilepsy; depression; anxiety and anxiety related disorders such as post-traumatic stress syndrome; tardive dyskinesia; psychosis related to depression, schizophrenia, bipolar disorder, mania, and drug intoxication or addiction; headache, including cluster headache, tension-type headache, and chronic daily headache; migraine; and acute and chronic pain states including severe pain, intractable pain, neuropathic pain, and post-traumatic pain.

More specifically, the present invention provides a method of treating or preventing pain or migraine comprising administering to a patient in need thereof an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof.

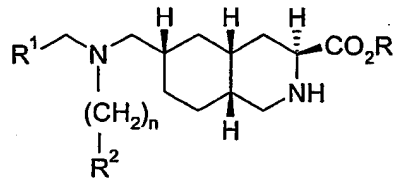
In addition, the present invention provides pharmaceutical compositions of compounds of Formula I including the pharmaceutically acceptable salts, prodrugs, and hydrates thereof, comprising, a compound of Formula I in combination with a pharmaceutically acceptable carrier, diluent or excipient. The present invention also encompasses novel intermediates, and processes for the synthesis of the compounds of Formula I and pharmaceutically acceptable salts or prodrugs thereof.

The present invention also provides the use of a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for treating or preventing a neurological disorder, or neurodegenerative condition. More specifically, the present invention provides the use of a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for treating or preventing pain or migraine.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds functional as iGluR5 receptor antagonists as well as pharmaceutically acceptable salts, prodrugs, and compositions thereof. These compounds are useful in treating or preventing neurological disorders, or neurodegenerative diseases, particularly pain and migraine. As such, methods for the treatment or prevention of neurological disorders, or neurodegenerative diseases, are also provided by the present invention. In addition, it should be understood by the skilled artisan that all of the compounds useful for the methods of the present invention are available for prodrug formulation. As used herein, the term "prodrug" refers to a compound of Formula I which has been structurally modified, for example a compound of Formula Ia, such that in vivo the prodrug is converted, for example, by hydrolytic, oxidative, reductive, or enzymatic cleavage into the parent compound (e.g. the carboxylic acid drug). As further shown in Scheme 1 below, compounds of Formula Ia where R is not hydrogen are converted in vivo, to form compounds of Formula I (a carboxylic acid). Such prodrugs may be, for example, metabolically labile ester derivatives of the parent compounds having a carboxylic acid group.

Scheme 1



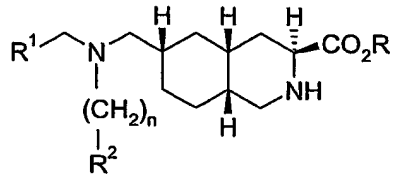
Ia

in vivo

I

It is to be understood that the present invention includes any such prodrugs, such as metabolically labile ester derivatives of compounds of Formula I. In all cases, the use of the compounds described herein as prodrugs is contemplated, and often is preferred, and thus, the prodrugs of all of the compounds provided are encompassed in the names of the compounds herein. Conventional procedures for the selection and preparation of suitable prodrugs are well known to one of ordinary skill in the art.

More specifically, examples of prodrugs of Formula I compounds which are understood to be included within the scope of the present invention, are represented by Formula Ia below:



Ia

wherein:

R^1, R^2 and n are as previously defined; and

R is (1-20C)alkyl, (2-6C)alkenyl, (1-6C)alkyl-aryl, (1-6C)alkyl-(3-10C)cycloalkyl, (1-6C)alkyl-N,N-(1-6C) dialkylamine, (1-6C)alkyl-pyrrolidine, (1-6C)alkyl-piperidine, or (1-6C)alkyl-morpholine.

It is understood that the iGluR5 receptor antagonists of the present invention may exist as pharmaceutically acceptable salts and, as such, salts are therefore included within the scope of the present invention. The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds provided by, or employed in the present invention which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

It will be understood by the skilled artisan that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free acids or bases. In all cases, the use of the pharmaceuticals described herein as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names therein.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, hydroiodide, dihydroiodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, α-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such

as hydrochloric acid, and those formed with organic acids such as maleic acid, mandelic acid, para-toluenesulfonic acid, and methanesulfonic acid.

Base addition salts include those derived from inorganic bases, such as ammonium, alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred. It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. It is further understood that such salts may exist as solvates. Preferred solvates include the hydrate.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers. The compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention. Preferred isomers include the 3S, 4aR, 6S, 8aR stereoisomers of compounds of Formula I or Formula Ia.

The specific stereoisomers and enantiomers of compounds of Formula I or Formula Ia can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by Eliel and Wilen, "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, Chapter 7, Separation of Stereoisomers. Resolution. Racemization, and by Collet and Wilen, "Enantiomers, Racemates, and Resolutions", John Wiley & Sons, Inc., 1981. For example, the specific stereoisomers and enantiomers can be prepared by stereospecific syntheses using enantiomerically and geometrically pure, or enantiomerically or geometrically enriched starting materials. In addition, the specific stereoisomers and enantiomers can be resolved and recovered by techniques such as chromatography on chiral stationary phases, enzymatic resolution or fractional recrystallization of addition salts formed by reagents used for that purpose.

The term "amine protecting group", as used herein, refers to those groups intended to protect or block the amine group against undesirable reactions during synthetic procedures and is designated structurally as (N)-Pg^1 where "Pg^1" is a suitable amine protecting group. Choice of a suitable amine protecting group used will depend upon the conditions that will be employed in subsequent reaction steps wherein protection is required, as is well within the knowledge of one of ordinary skill in the art. Commonly used amine protecting groups are disclosed in T.W. Greene and P.G.M. Wuts, Protective Groups In Organic Synthesis, 3rd Ed. (John Wiley & Sons, New York (1999)). Suitable amine protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, alpha-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like, carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, alpha,

alpha-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; arylalkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred suitable amine protecting groups are formyl, acetyl, methyloxycarbonyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, allyloxycarbonyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) The amine protecting group may be removed by using a conventional procedure which does not affect another portion of the molecule. Alternatively, the amine protecting group may be removed by using a procedure that also removes other protecting groups such as the carboxyl protecting group.

The term "carboxyl protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups of the compound and is designated structurally as (COO)-Pg^2 where "Pg^2" is a suitable carboxyl protecting group. Particular values of carboxyl protecting groups include, for example, methyl, ethyl, tert-butyl, benzyl, methoxymethyl, trimethylsilyl, allyl and the like. Further examples of such groups may be found in T.W. Greene and P.G.M. Wuts, Protecting Groups in Organic Synthesis, 3rd. Ed. (John Wiley & Sons, N.Y. (1999). The carboxyl protecting group may be removed by using a conventional procedure which does not affect another portion of the molecule. Alternatively, the carboxyl protecting group may be removed by using a procedure that also removes other protecting groups such as the amine protecting group.

As used herein the term "(1-4C)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like.

As used herein the term "(1-6C)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to methyl,

ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, and the like. Particular values of (1-6C)alkyl include 2-ethylbutyl. It is understood that the term "(1-4C)alkyl" is included within the definition of "(1-6C)alkyl".

As used herein the term "(1-10C)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 10 carbon atoms and includes, but is not limited to methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like. It is understood that the terms "(1-4C)alkyl" and "(1-6C)alkyl" are included within the definition of "(1-10C)alkyl".

As used herein the term "(1-20C)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 20 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, 3-methylpentyl, 2-ethylbutyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-heptadecyl, n-nonadecyl, n-eicosyl and the like. It is understood that the terms "(1-4C)alkyl", "(1-6C)alkyl", and "(1-10C)alkyl" are included within the definition of "(1-20C)alkyl".
As used herein, the terms "Me", "Et", "Pr", "iPr", "Bu" and "t-Bu" refer to methyl, ethyl, propyl, isopropyl, butyl and tert-butyl respectively.

As used herein, the term "(1-4C)alkoxy" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is not limited to methyoxy, ethyoxy, n-propoxy, isopropoxy, n-butoxy, and the like.

As used herein the term "(1-6C)alkoxy" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, n-pentoxy, n-hexoxy, and the like. It is understood that the terms "(1-4C)alkoxy" is included within the definition of "(1-6C)alkoxy".

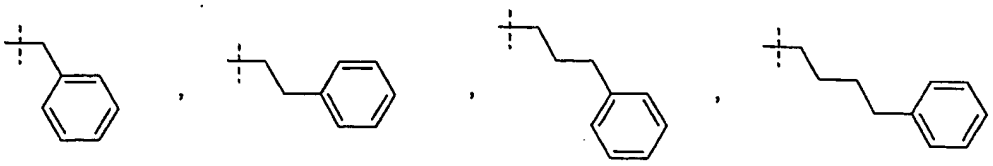
As used herein, the term "(1-6C)alkyl-(1-6C)alkoxy" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a (1-6C)alkoxy group attached to the aliphatic chain.

As used herein, the terms "Halo", "Halide" or "Hal" refer to a chlorine, bromine, iodine or fluorine atom, unless otherwise specified herein.

As used herein the term "(2-6C)alkenyl" refers to a straight or branched, monovalent, unsaturated aliphatic chain having from two to six carbon atoms. Typical (2-6C) alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

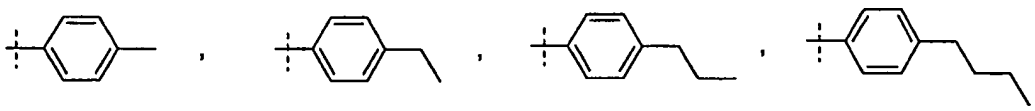
As used herein, the term "aryl" refers to a monovalent carbocyclic group containing one or more fused or non-fused phenyl rings and includes, for example, phenyl, 1- or 2-naphthenyl, dihydronaphthenyl, tetrahydronapthyl and the like. The term "substituted aryl" refers to an aryl group substituted with one or two moieties chosen from the group consisting of phenyl, halogen, hydroxy, cyano, nitro, (1-6C)alkyl, (1-4C)alkoxy, (1-6C)alkyl(3-10C)cycloalkyl, (1-6C)alkylaryl, (1-6C)alkoxycarbonyl, protected carboxyl, carboxymethyl, hydroxymethyl, amino, aminomethyl, trifluoromethoxy or trifluoromethyl. Included within the term "substituted aryl" are 2-methylphenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,4-dimethylphenyl, 2,3-difluorophenyl, 2-trifluoromethylphenyl, 4-biphenyl, 2,4-difluorophenyl, 2-methoxyphenyl, 2,3-dichlorophenyl, 4-trifluoromethoxyphenyl, 2-fluorophenyl, 2-trifluoromethoxyphenyl, 6-hydroxynapthalen-2-yl, 3-fluorophenyl, 3,4-dichlorophenyl, 3-trifluoromethoxyphenyl, 4-fluorophenyl, 2-biphenyl, 4-methylphenyl, 2,3-dimethylphenyl, 2,5-dimethylphenyl, 3-methylphenyl, 3-chlorophenyl and 3-biphenyl.

As used herein, the term "(1-6C)alkyl-aryl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an aryl group attached to the aliphatic chain. Included within the term "(1-6C)alkyl-aryl" are the following:



and the like.

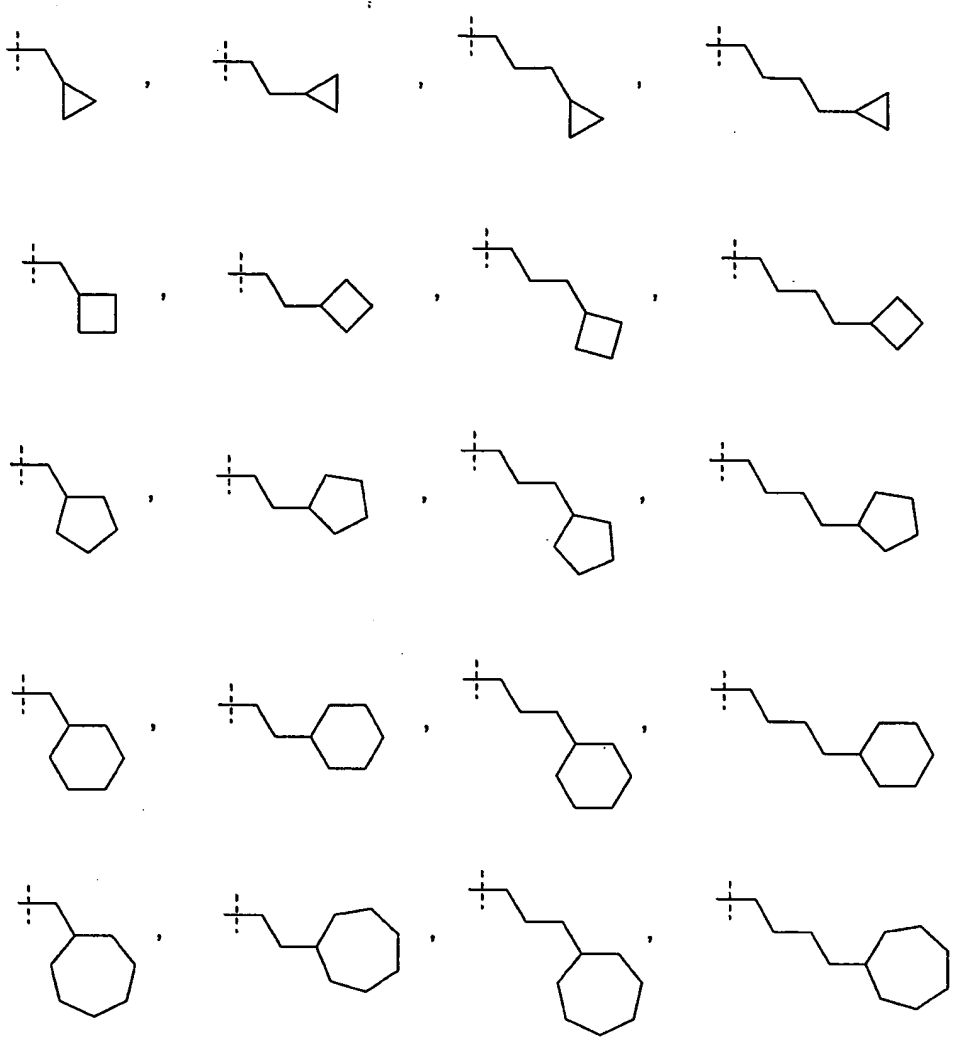
As used herein, the term "aryl-(1-6C)alkyl" refers to an aryl group which has a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms attached to the aryl group. Included within the term "aryl-(1-6C)alkyl" are the following:



and the like.

As used herein the term "(3-10C)cycloalkyl" refers to a saturated hydrocarbon ring structure composed of one or more fused or unfused rings containing from three to ten carbon atoms. Typical (3-10C) cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantanyl, and the like.

As used herein, the term "(1-6C)alkyl-(3-10C)cycloalkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a (3-10C)cycloalkyl attached to the aliphatic chain. Included within the term "(1-6C)alkyl-(3-10C)cycloalkyl" are the following:



and the like.

As used herein, the term "(1-6C) alkoxycarbonyl" refers to a carbonyl group having a (1-6C)alkyl group attached to the carbonyl carbon through an oxygen atom. Examples of this group include t-buoxycarbonyl, methoxycarbonyl, and the like.

As used herein the term "heterocycle" refers to a five- or six-membered ring, which contains one to four heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen. The remaining atoms of the ring are recognized as carbon by those of skill in the art. Rings may be saturated or unsaturated. Examples of heterocycle groups include thiophenyl, furyl, pyrrolyl, imidazolyl, pyrrazolyl, thiazolyl, thiazolidinyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridiazinyl, triazinyl, imidazolyl, dihydropyrimidyl,

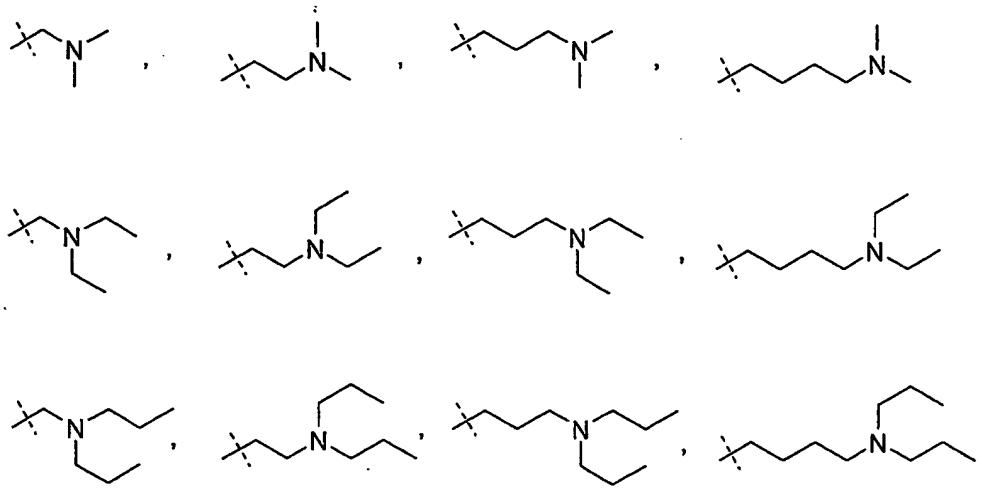
tetrahydropyrimdyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrazolidinyl, pyrimidinyl, imidazolidinyl, morpholinyl, pyranyl, thiomorpholinyl, and the like. As used herein, the term "substituted heterocycle" represents a heterocycle group substituted with one or two moieties chosen from the group consisting of aryl, halogen, hydroxy, cyano, nitro, oxo, (1-6C)alkyl, (1-4C)alkoxy, 1-6C alkyl(3-10C)cycloalkyl, (1-6C)alkylaryl, (1-6C)alkoxycarbonyl, protected carboxyl, carboxyl, carboxymethyl, hydroxymethyl, amino, aminomethyl, or trifluoromethyl. Examples of substituted heterocyle include hydroxyisoxazole, methoxyisoxazole, 1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid and the like. Further, the heterocycle group can be optionally fused with one or two aryl groups to form a benzo-fused heterocylic group. Examples of benzo-fused heterocycles include benzofuranyl, indolyl, quinolinyl, isoquinoilinyl and benzothienyl, and the like. The benzo-fused heterocycle may be optionally saturated either partially or fully. Examples of partially saturated benzo-fused heterocyles include tetrahydroisoquinoline and the like. Examples of fully saturated benzofused heterocycles include decahydroisoquinoline and the like.

As used herein, the term "(1-6C)alkyl-heterocycle" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms bearing a heterocycle group. Further, as used herein, the term "(1-6C)alkyl-(substituted)heterocycle" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms bearing a substituted heterocycle group.

As used herein, the term "(1-6C)alkyl-tetrazole" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms bearing a tetrazole group.

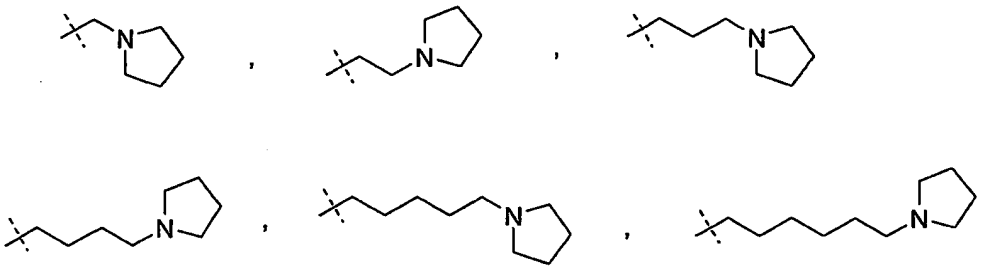
As used herein the term "N,N-(1-6C)dialkylamine" refers to a nitrogen atom substituted with two straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms. Included within the term "N,N-(1-6C) dialkylamine" are –N(CH3)2, -N(CH2CH3)2, -N(CH2CH2CH3)2, -N(CH2CH2CH2CH3)2, and the like.

As used herein the term "(1-6C)alkyl-N,N-(1-6C)dialkylamine" refers to straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an N,N-(1-6C)dialkylamine attached to the aliphatic chain. Included within the term "1-6C alkyl-N,N-(1-6C)dialkylamine" are the following:



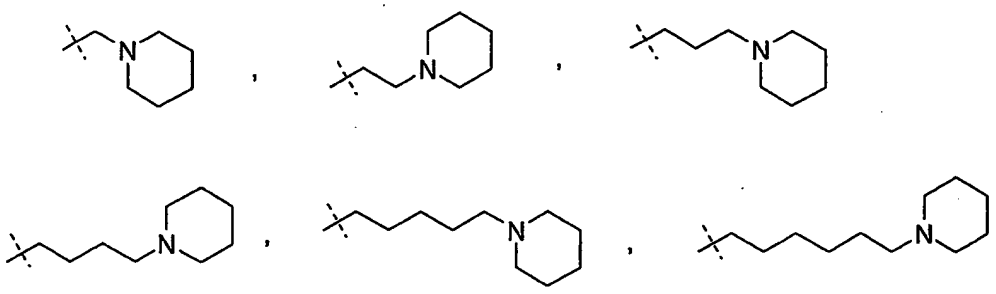
and the like.

As used herein the term "(1-6C)alkyl-pyrrolidine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a pyrrolidine attached to the aliphatic chain. Included within the scope of the term "(1-6C)alkyl-pyrrolidine" are the following:



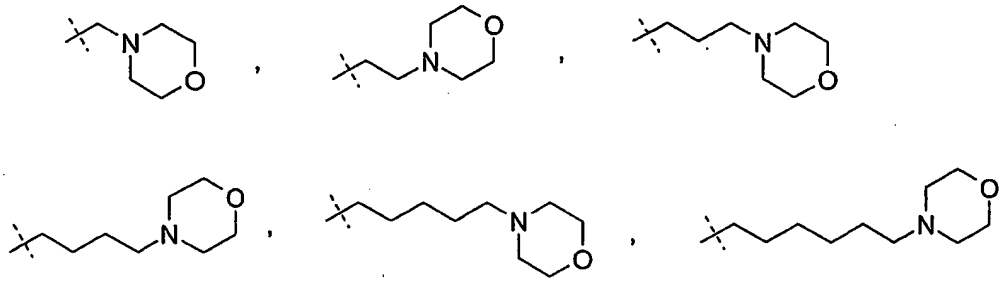
and the like.

As used herein the term "(1-6C)alkyl-piperidine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a piperidine attached to the aliphatic chain. Included within the scope of the term "(1-6C)alkyl-piperidine" are the following:



and the like.

As used herein the term "(1-6C)alkyl-morpholine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a morpholine attached to the aliphatic chain. Included within the scope of the term "(1-6C)alkyl-morpholine" are the following:



and the like.

An enclosed solid wedge refers to a bond that protrudes forward out of the plane of the page toward the reader's eye.

An open dashed wedge refers to a bond that protrudes backward out of the plane of the page away from the reader's eye.

As used herein the term "iGluR5" refers to the kainate ionotropic glutamate receptor, subtype 5, of the larger class of excitatory amino acid receptors.

As used herein the term "migraine" refers a disorder of the nervous system characterized by recurrent attacks of head pain (which are not caused by a structural brain abnormalitiy such as those resulting from tumor or stroke), gastrointestinal disturbances, and possibly neurological symptoms such as visual distortion. Characteristic headaches of migraine usually last one day and are commonly accompanied by nausea, emesis, and photophobia. Migraine may represent a "chronic" condition, or an "acute" episode. The

term "chronic", as used herein, means a condition of slow progress and long continuance. As such, a chronic condition is treated when it is diagnosed and treatment continued throughout the course of the disease. Conversely, the term "acute" means an exacerbated event or attack, of short course, followed by a period of remission. Thus, the treatment of migraine contemplates both acute events and chronic conditions. In an acute event, compound is administered at the onset of symptoms and discontinued when the symptoms disappear. As described above, a chronic condition is treated throughout the course of the disease.

As used herein the term "patient" refers to a mammal, such a mouse, gerbil, guinea pig, rat, dog or human. It is understood, however, that the preferred patient is a human.

The term "iGluR5 receptor antagonist" or "iGluR5 antagonist", as used herein, refers to those excitatory amino acid receptor antagonists which bind to, and antagonize the activity of the iGluR5 kainate receptor subtype whether administered alone, or as a combination of compounds capable of acting as an iGluR5 receptor antagonist. As a preferred embodiment, the present invention further provides selective iGluR5 receptor antagonists. "Selective iGluR5 receptor antagonist" or "selective iGluR5 antagonist" as used herein, includes those excitatory amino acid receptor antagonists which selectively bind to, and antagonize, the iGluR5 kainate receptor subtype, relative to the iGluR2 AMPA receptor subtype. Preferably the "iGluR5 antagonists" for use according to the methods of the present invention have a binding affinity at least 5 fold greater for iGluR5 than for iGluR2, more preferably at least 10 fold greater and most preferably 100 fold greater. WO 98/45270 provides examples of selective iGluR5 receptor antagonists and discloses methods for synthesis thereof.

As used herein, the terms "treating", "treatment", or "to treat" each mean to alleviate symptoms, eliminate the causation of resultant symptoms either on a temporary or permanent basis, and to prevent, slow the appearance, or reverse the progression or severity of resultant symptoms of the named disorder. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

As used herein the term "effective amount" refers to the amount or dose of the compound, upon single or multiple dose administration to the patient, which provides the

desired effect in the patient under diagnosis or treatment. An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose of compound administered, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the degree of involvement or the severity of the disease involved; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of each compound used in the present method of treatment. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg.

Oral administration is a preferred route of administering the compounds employed in the present invention whether administered alone, or as a combination of compounds capable of acting as an iGluR5 receptor antagonist. Oral administration, however, is not the only route, nor even the only preferred route. Other preferred routes of administration include transdermal, percutaneous, pulmonary, intravenous, intramuscular, intranasal, buccal, sublingual, or intrarectal routes. Where the iGluR5 receptor antagonist is administered as a combination of compounds, one of the compounds may be administered by one route, such as oral, and the other may be administered by the transdermal, percutaneous, pulmonary, intravenous, intramuscular, intranasal, buccal, sublingual, or intrarectal route, as particular circumstances require. The route of administration may be varied in any way, limited by the physical properties of the compounds and the convenience of the patient and the caregiver.

The compounds employed in the present invention may be administered as pharmaceutical compositions and, therefore, pharmaceutical compositions incorporating compounds of Formula I, Formula Ia or pharmaceutically acceptable salts thereof are important embodiments of the present invention. Such compositions may take any

physical form that is pharmaceutically acceptable, but orally administered pharmaceutical compositions are particularly preferred. Such pharmaceutical compositions contain, as an active ingredient, an effective amount of a compound of Formula I or Formula Ia, including the pharmaceutically acceptable salts and hydrates thereof, which effective amount is related to the daily dose of the compound to be administered. Each dosage unit may contain the daily dose of a given compound, or may contain a fraction of the daily dose, such as one-half or one-third of the dose. The amount of each compound to be contained in each dosage unit depends on the identity of the particular compound chosen for the therapy, and other factors such as the indication for which it is given. The pharmaceutical compositions of the present invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing well known procedures.

Compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg of each compound individually or in a single unit dosage form, more preferably about 5 to about 300 mg (for example 25 mg). The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for a patient, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient.

The inert ingredients and manner of formulation of the pharmaceutical compositions are conventional. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compound, however, is best defined as the "effective amount", that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the compounds employed in the present invention do not depend on the

nature of the composition, hence, the compositions are chosen and formulated solely for convenience and economy.

Particular Aspects the Compounds of the Invention

The following list sets out several groupings of particular substituents and particular variables for the compounds of Formula I and Formula Ia. It will be understood that such particular substituents and variables represent particular aspects of the compounds of the present invention. It will be further understood that each of these groupings may be combined or rearranged, with other provided groupings, to create still additional particular aspects of the present invention.

Thus, a particular aspect of the present invention is one wherein the compound is a compound of Formula I or Formula Ia, wherein:

(a) R^1 is 3-hydroxyisoxazol-5-yl.

(b) R^1 is tetrazol-5-yl.

(c) R^2 is phenyl, napthalen-1-yl, napthalen-2-yl, or napthalen-3-yl; an aryl substituted with one or two moeities selected from phenyl, halogen, hydroxy, (1-6C)alkyl, (1-4C)alkoxy, trifluoromethoxy or trifluoromethyl; (3-10C)cycloalkyl;
benzothiophenyl, thiophenyl, decahydroisoquinolinyl, tetrazolyl, or hydroxyisoxazolyl.

(d) R^2 is phenyl, napthalen-1-yl, napthalen-2-yl, napthalen-3-yl.

(e) R^2 is phenyl, napthalen-1-yl, or napthalen-2-yl.

(f) R^2 is an aryl substituted with one or two moeities selected from phenyl, halogen, hydroxy, (1-6C)alkyl, (1-4C)alkoxy, trifluoromethoxy or trifluoromethyl.

(g) R^2 is 2-methylphenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,4-dimethylphenyl, 2,3-difluorophenyl, 2-trifluoromethylphenyl, 4-biphenyl, 2,4-difluorophenyl, 2-methoxyphenyl, 2,3-dichlorophenyl, 4-trifluoromethoxyphenyl, 2-

fluorophenyl, 2-trifluoromethoxyphenyl, 6-hydroxynapthalen-2-yl, 3-fluorophenyl, 3,4-dichlorophenyl, 3-trifluoromethoxyphenyl, 4-fluorophenyl, 2-biphenyl, 4-methylphenyl, 3-biphenyl, 2,3-dimethylphenyl, 2,5-dimethylphenyl, 3-methylphenyl, 3-chlorophenyl.

(h) R^2 is (3-10C)cycloalkyl.

(i) R^2 is cyclohexyl.

(j) R^2 is benzothiophenyl, thiophenyl, decahydroisoquinolinyl, or tetrazolyl.

(k) R^2 is benzothiophen-2-yl, thiophen-2-yl, or tetrazol-5-yl.

(l) R is (1-20C)alkyl.

(m) R is (1-10C)alkyl.

(n) R is (1-6C)alkyl.

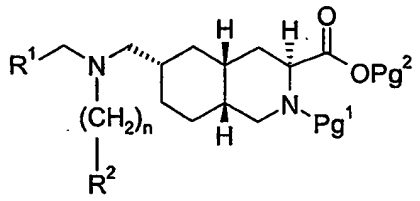
(o) R is methyl, ethyl, or 2-ethyl butyl.

(p) n is 1.

A compound of Formula I, Formula Ia, or pharmaceuticaly acceptable salts thereof, may be made by a process which is analogous to one known in the chemical art for the production of structurally analogous compounds or by a novel process described herein. Such processes and intermediates useful for the manufacture of a compound of Formula I, Formula Ia, or pharmaceutically acceptable salts thereof, as defined above, are provided as further features of the invention and are illustrated by the following procedures in which, unless otherwise specified, the meanings of the generic radicals are as defined above.

(A) Compounds of Formula Ia: Compounds of Formula Ia may be synthesized by esterifing a compound of Formula I as described in the procedures for Examples.

(B) Compounds of Formula I: Compounds of Formula I may be synthesized by deprotecting a compound of Formula V



V

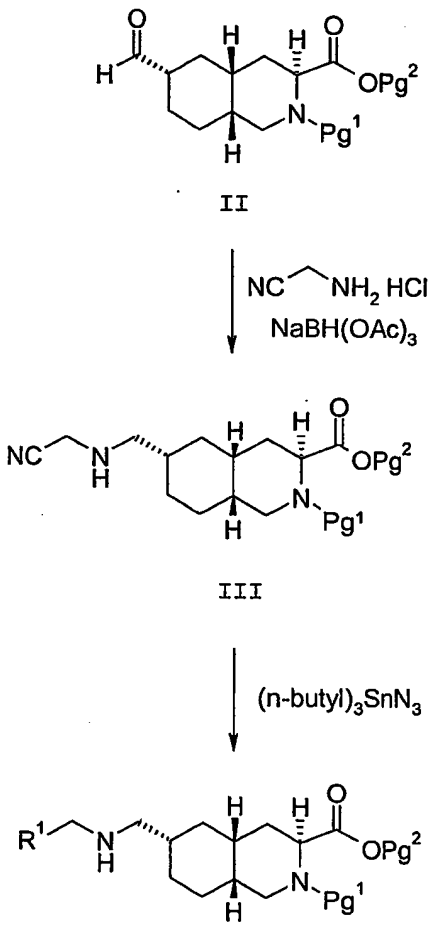
wherein Pg^1 is an amine protecting group and Pg^2 is a carboxyl protecting group as described in the procedures for Examples.

Compounds of Formula I, Formula Ia, or pharmaceutically acceptable salts thereof can be prepared, for example, by following the procedures set forth in the Schemes below. All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art. For example, certain starting materials can be prepared by one of ordinary skill in the art following procedures disclosed in United States Patent Nos. 5,356,902 (issued October 18, 1994); 5,446,051 (issued August 29, 1995); and 5,670,516 (issued September 23, 1997). Other necessary starting materials for the below procedures may be made by procedures which are selected from standard techniques of organic and heterocyclic chemistry, techniques which are analogous to the syntheses of known structurally similar compounds, and the procedures described in the Examples, including novel procedures.

Generally, compounds of Formula I where R^1 is tetrazol-5-yl may be prepared by reacting compounds of Formula II in a series of steps outlined in schemes 2 and 3. Compounds of Formula II may be prepared by one of ordinary skill in the art following procedures disclosed in United States Patents No. 5,670,516 (issued September 23, 1997).

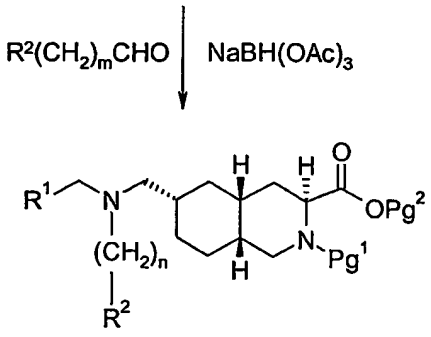
More specifically, compounds of Formula II are reacted with aminoacetonitrile in the presence of a suitable reducing agent such as sodium triacetoxyborohydride in a solvent such as 1,2-dichloroethane to provide compounds of Formula III. The reaction is conveniently carried out in the presence of a base such as triethylamine. Compounds of Formula III are reacted with a suitable azide agent such as azido-tributylstannane in a solvent such as toluene to provide compounds of Formula IV (see Scheme 2).

Scheme 2



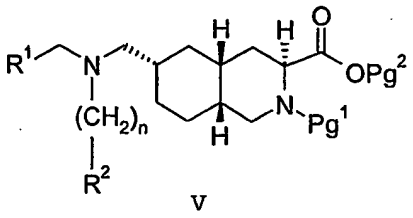
In Scheme 3, compounds of Formula IV are reacted with an aldehyde of Formula $R^2(CH_2)_mCHO$ where m is 0 or 1, and a suitable reducing agent such as sodium triacetoxyborohydride in a solvent such as 1,2-dichloroethane to provide compounds of Formula V where R^1 is tetrazol-5-yl. The reaction is conveniently carried out in the presence of an acid such as acetic acid.

Scheme 3

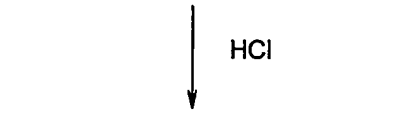


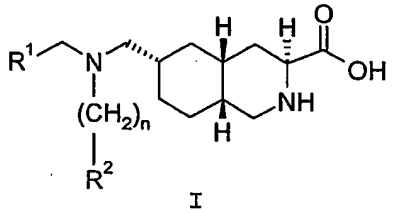
In scheme 4, compounds of Formula V are reacted with a suitable deprotecting agent such as hydrochloric acid to provide compounds of Formula I. Compounds of Formula Ia may be prepared by esterifiying compounds of Formula I with agents such as an alcohol of Formula ROH. The esterifiying reaction is conveniently carried out in the presence of an activating agent such as thionyl chloride.

Scheme 4

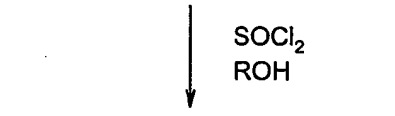


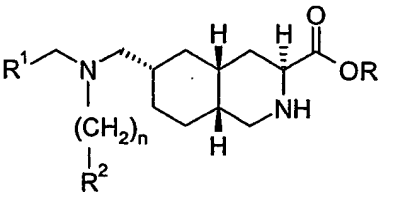
V





I





Ia

Compounds of Formula I where R^1 is tetrazol-5-yl or 3-hydroxyisoxazol-5-yl may be prepared by reacting compounds of Formula VI where X is a suitable leaving group in a series of steps outlined in schemes 5, 6 and 7. The choice of a suitable leaving group is well within the knowledge of the skilled artisan. For example, compounds of Formula VI may be prepared by one of ordinary skill in the art following procedures disclosed in the Journal of Organic Chemistry, 1994, 59, pp. 7862-7869 where X is iodo; or WO 0101972 (June 27, 2000) where X is para-toluenesulphonate.

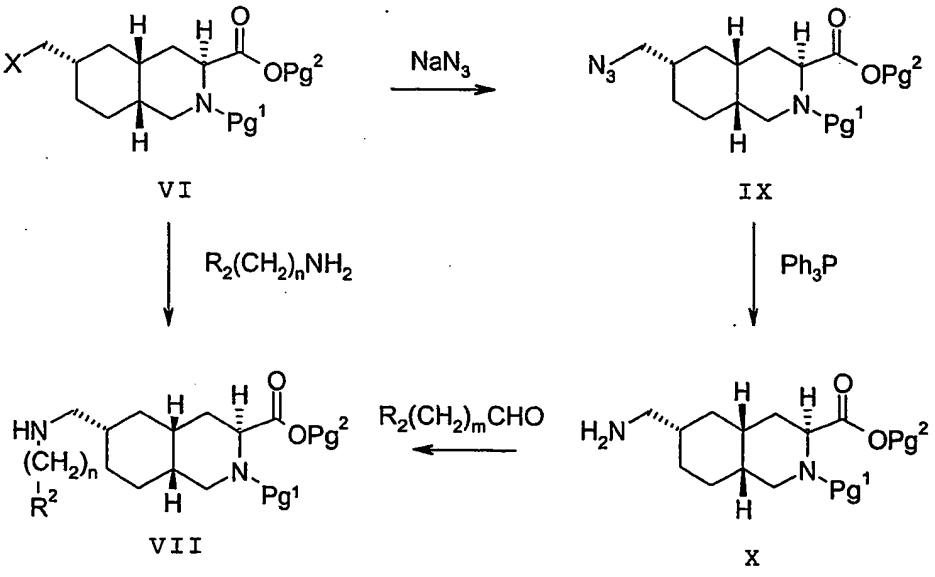
More specifically, compounds of Formula VI are reacted with an amine of the Formula $R^2(CH_2)_nNH_2$ in a suitable solvent such as dimethylforamide to provide compounds of Formula VII (see scheme 5). The reaction is conveniently carried out in the presence of a base such as potassium carbonate.

Alternatively, compounds of Formula VII may be prepared by reacting compounds of Formula VI in a two step sequence also shown in scheme 5. More specificly, compounds of Formula VI are reacted with an azide salt such as sodium azide in a suitable solvent such as dimethylformamide to provide compounds of Formula IX.

Compounds of Formula IX are reacted with a suitable reducing agent such as triphenylphosphine in a solvent such as tetrahydrofuran to provide compounds of Formula X.

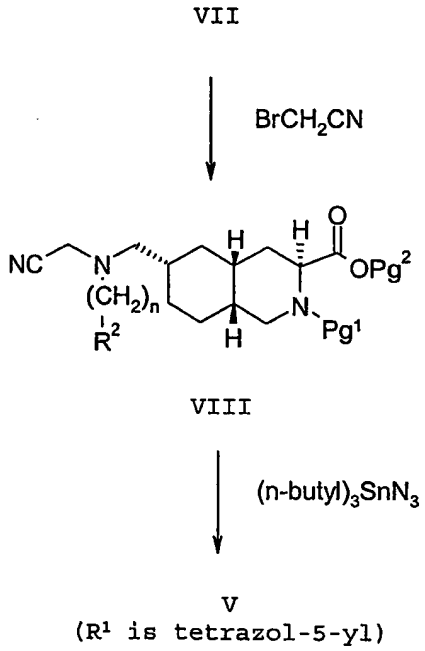
Compounds of Formula X are reacted with an aldehyde of Formula $R^2(CH_2)_mCHO$ where m is 0 or 1, and a suitable reducing agent such as sodium triacetoxyborohydride in a solvent such as 1,2-dichloroethane to provide compounds of Formula VII. The reaction is conveniently carried out in the presence of an acid such as acetic acid.

Scheme 5



In scheme 6, compounds of Formula VII are reacted with a haloacetonitrile such as bromoacetonitrile in a suitable solvent such as acetonitrile to provide compounds of Formula VIII. The reaction is conveniently carried out in the presence of a base such as sodium bicarbonate. Compounds of Formula VIII are reacted with a suitable azide agent such as azido-tributylstannane to provide compounds of Formula V where R^1 is tetrazol-5-yl.

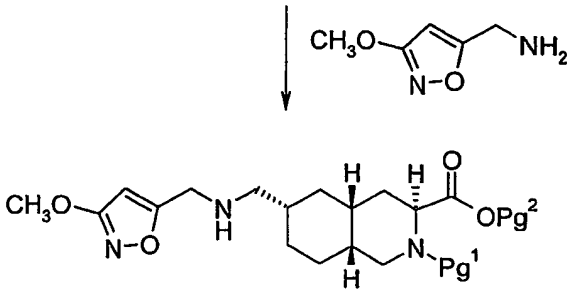
Scheme 6



In scheme 7, compounds of Formula VI are reacted with a hydroxyl protected aminomethylisoxazole such as 3-methoxy-5-aminomethylisoxazole (Pevarello and Varasi, Synth. Commun., (1992), 22, p. 1939) in a suitable solvent such as acetonitrile to provide a mixture of compounds of Formulas XI and XII. The reaction is conveniently carried out in the presence of a base such as potassium carbonate. The mixture is separated using standard purification techniques know to the skilled artisan such as silica gel chromatography.

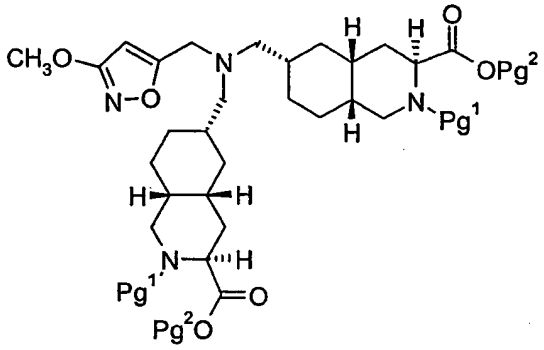
Scheme 7

VI



XI

+

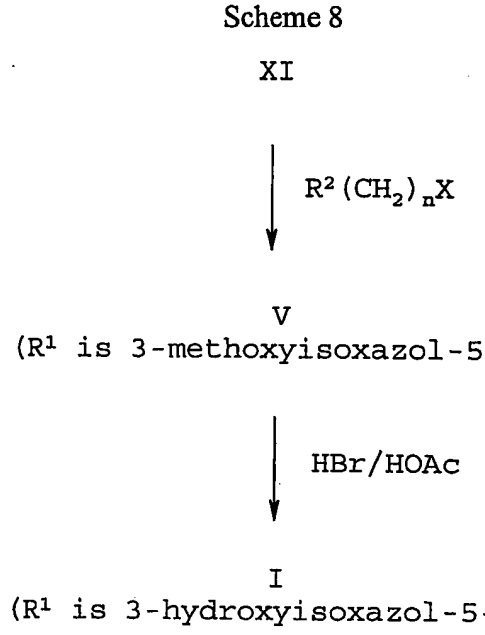


XII

In scheme 8, compounds of Formula XI are reacted with compounds of Formula $R^2(CH_2)_nX$ where X is a suitable leaving group such as bromo to provide compounds of Formula V where R^1 is 3-methoxyisoxazol-5-yl. The reaction is carried out in a solvent such as acetonitrile and a suitable base such as potassium carbonate.

Compounds of Formula V where R^1 is a hydroxyl protected aminomethylisoxazole such as 3-methoxyisoxazol-5-yl are reacted with deprotecting agents such hydrogen bromide in a suitable solvent such as acetic acid to provide compounds of Formula I where R^1 is 3-hydroxyisoxazol-5-yl.

Scheme 8



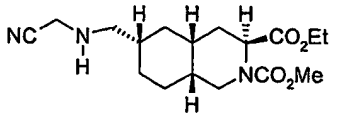
Compounds of Formula XII are reacted with deprotecting agents such hydrogen bromide in a suitable solvent such as acetic acid to provide compounds of Formula I where R^1 is 3-hydroxyisoxazol-5-yl, n is 1, and R^2 is 3S, 4aR, 6S, 8aR 6-methyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic acid.

The following examples illustrate the methods of the present invention. The reagents and starting materials are readily available to one of ordinary skill in the art. These examples are intended to be illustrative only and are not to be construed so as to limit the scope of the invention in any way. As used herein, the following terms have the meanings indicated: "i.v." refers to intravenously; "p.o." refers to orally; "i.p." refers to intraperitoneally; "eq" or "equiv." refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "L" refers to liters; "mL" refers to milliliters; "uL" refers to microliters; "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "mm Hg" refers to millimeters of mercury; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers

to retention factor; "R_t" refers to retention time; "□" refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to dimethyl sulfoxide; "aq" refers to aqueous; "EtOAc" refers to ethyl acetate; "iPrOAc" refers to isopropyl acetate; "MeOH" refers to methanol; "MTBE" refers to tert-butyl methyl ether; "RT" refers to room temperature; "Ki" refers to the dissociation constant of an enzyme-antagonist complex and serves as an index of ligand binding; and "ID_{50}" and "ID_{100}" refer to doses of an administered therapeutic agent which produce; respectively, a 50 % and 100% reduction in a physiological response.

Preparation 1

Ethyl (3S, 4aR, 6S, 8aR)-6-[(cyanomethyl-amino)-methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate

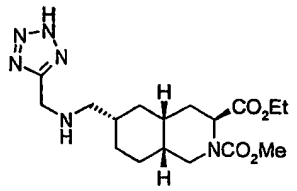


To a solution of aminoacetonitrile hydrochloride (2.49 g, 26.9 mmol) in dry 1,2-dichloroethane (80 mL) at room temperature is added triethylamine (3.7 mL, 26.9 mmol). After stirring 30 min., the mixture is filtered and the filtrate solution added via syringe to a solution of ethyl (3S, 4aR, 6S, 8aR)-6-formyl-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (US patent 5,356,902)(4.0 g, 13.45 mmol, 1.0 eq.) in 50 ml of 1,2-dichloethane at room temperature. The resulting reaction mixture is allowed to stir for 2h. Sodium triacetoxyborohydride (7.99 g, 37.7 mmol) is added. After stirring for 2h 30 min., the reaction mixture is poured into a saturated aqueous solution of sodium bicarbonate (200 mL) and stirred for a few minutes. The layers are separated and the aqueous phase is extracted with two portions of dichloromethane. The combined organic extracts are dried over magnesium sulfate, filtered and concentrated to dryness. Flash chromatography (silica gel, hexane-ethyl acetate 1:1) provides 2.61 g (54% yield) of the title compound as a colorless oil.

Ion Electrospray Mass Spectrum M+1 :338

Preparation 2

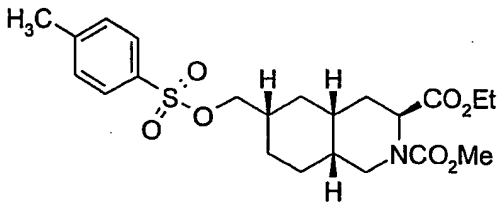
Ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



To a solution of 6.78 g (19 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-[(cyanomethyl-amino)-methy]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 1) in toluene (3 mL) at room temperature is added azido-tri-n-butylstannane (15.61 mL, 57 mmol). The reaction is heated at 80 °C overnight, cooled to room temperature and quenched with 1 N aqueous solution of hydrochloric acid (30 mL). The mixture is stirred for 2 hours at room temperature and concentrated to dryness. The resulting residue is dissolved in water and Dowex 50x 8-100 (150 g) is added. After stirring overnight, the mixture is filtered and the resin is washed with tetrahydrofuran (3x250 mL) and water (5x250 mL). The filtered resin is suspended in water/pyridine 9:1 and stirred for 48 hours. The suspension is filtered and washed with water. The filtrate is concentrated to dryness to give 3.97 g (55% yield) of the title compound.
Ion Electrospray Mass Spectrum M+1 :381

Preparation 3

3S, 4aR, 6S, 8aR Ethyl 6-((4-Methylphenyl)sulfonyloxy) methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate



To a solution of 15.0 g (50.1 mmol) of 3S, 4aR, 6S, 8aR ethyl 6-hydroxymethyl-2-methoxycarbonyl-decahydroisoquinoline-3-carboxylate (may be prepared following the procedures described in United States Patent No. 5,670,516) in dichloromethane (100 mL) with cooling to 0°C is added triethylamine (20.9 mL, 150.3 mmol). A solution of p-toluenesulfonyl chloride (19.1 g, 100.2 mmol) in dichloromethane (100 mL) is added and the reaction is allowed to stir for 16 h at room temperature. A 10% solution of sodium hydrogen sulfate is added and the resulting mixture is extracted with two portions of dichloromethane. The combined organic extracts are dried over magnesium sulfate, filtered, and concentrated to dryness. The resulting residue is purified by column chromatography eluting with 10–50% ethyl acetate/hexanes to provide 20.1 g (89%) of the title compound as a colorless oil.

mass spectrum (ion-spray): m/z = 451.5 (M+1)

Analysis cald for $C_{22}H_{31}NO_7S \cdot 0.25\ H_2O$:

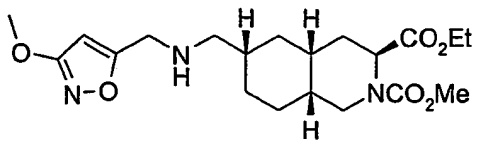
Theory: C, 57.69; H, 6.93; N, 3.06

Found: C, 57.76; H, 6.93; N, 3.35

^{13}C NMR: δ (DMSO-d_6, ppm) 171.4, 144.8, 132.4, 130.1, 127.6, 74.6, 60.4, 53.1, 52.4, 44.1, 34.6, 31.8, 31.0, 29.8, 28.8, 24.9, 23.3, 21.0, 14.0.

Preparation 4

3S, 4aR, 6S, 8aR Ethyl 6-(((3-Methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate



To 3S, 4aR, 6S, 8aR ethyl 6-((4-Methylphenyl) sulfonyloxy)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (preparation 3) (8.50 g, 18.7 mmol), *C*-(3-Methoxyisoxazol-5-yl)-methylamine (may be prepared according to the procedure of Pevarello, P.; Varasi, M.; Synth. Commun., **1992**, *22*, 1939) (2.0 g, 15.6 mmol), and potassium carbonate (3.23 g, 23.4 mmol) in a pressure vessel is added acetonitrile (15 mL) at room temperature. The reaction is purged with nitrogen, sealed and heated at 80°C for 5 days. After cooling to room temperature, dichloromethane (25 mL) and water (50 mL) are added and the layers separated. The aqueous phase is extracted with two portions of dichloromethane. The combined organic extracts are dried over magnesium sulfate, filtered, and concentrated to dryness. The resulting residue is purified by column chromatography eluting with 25-75% ethyl acetate/hexanes) to provide 2.81 g (44%) of the title compound.

mass spectrum (ion-spray): m/z = 410.3 (M+1)

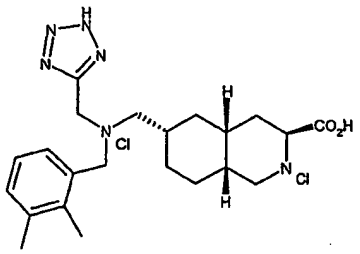
Analysis cald for $C_{20}H_{31}N_3O_6 \cdot 0.1C_4H_8O_2$:

Theory: C, 58.58, H, 7.66, N, 10.05

Found: C, 58.21, H, 7.52, N, 10.09

Example 1

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(2,3-dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]- methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl(3S, 4aR, 6S, 8aR)-6-{[(2,3-dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

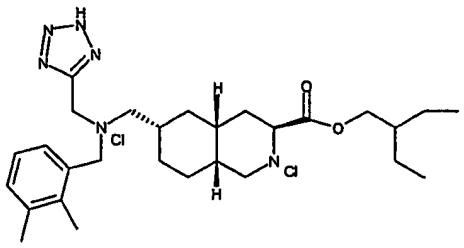
To a solution of 1.30 g (3.42 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) in 50 mL of 1,2-dichloroethane at room temperature is added 2,3-dimethylbenzaldehyde (800 mg, 5.96 mmol) and acetic acid (1.18 mL, 20.62 mmol). After stirring 3 hours, 2.01 g (9.57 mmol) of sodium triacetoxyborohydride is added. The reaction mixture is stirred overnight at room temperature, quenched with a saturated solution of sodium bicarbonate and extracted with three portions of ethyl acetate. The combined organic extracts are dried over sodium sulfate, filtered and concentrated to dryness. The crude reaction product is purified by flash chromatography (Silica gel, ethyl acetate, ethyl acetate-acetic acid, 10:1) to afford 1.53g (65% yield) of the title compound.
Ion Electrospray Mass Spectrum M+1 :499

B. (3S, 4aR, 6S, 8aR)-6-{[(2,3-Dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

A mixture of 1.00 g (2.00 mmol) of ethyl(3S, 4aR, 6S, 8aR)-6-{[(2,3-dimethyl-benzyl)-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 1A) and 3N hydrochloric acid (20 ml) is heated at 100°C overnight. The reaction mixture is cooled to room temperature and washed with two portions of ethyl acetate. The aqueous layer is concentrated to dryness. The resulting residue is partially dissolved in water and concentrated to dryness (3 times) to afford 903 mg (93% yield) of the title compound.
1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.56 (d, J = 6.5 Hz, 1 H); 7.33-7.19 (m, 2 H); 4.85 (s, 2 H); 4.65 (s, 2 H); 4.00 (d, J = 12.6 Hz, 1 H); 3.27-3.01 (m, 4 H); 2.34 (s, 3 H); 2.33 (s, 3 H); 2.15-1.99 (m, 6 H); 1.70-1.58 (m, 4 H); 1.10-1.10 (m, 1 H).
Ion Electrospray Mass Spectrum M –2HCl +1: 413

Example 2

Preparation of 2-ethylbutyl (3S, 4aR, 6S, 8aR)-6-{[(2,3-dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.



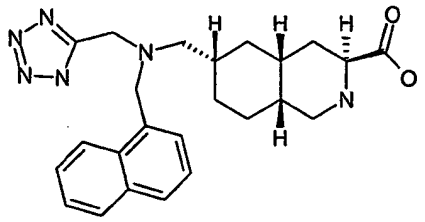
To a solution of 800 mg (1.64 mmol) of (3S, 4aR, 6S, 8aR)-6-{[(2,3-dimethyl-benzyl)-(1(2)H-tetrazol-5-ylmethyl)-amino]- methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride (Example 1) in 5 mL of 2-ethyl butanol at room temperature is added thionyl chloride (1.4 mL, 18.12 mmol). The mixture is heated at 120 °C for 3 hours, cooled to room temperature, and evaporated to dryness. The resulting residue is washed with ether to afford 934 mg (65% yield) of the title compound.

1H-NMR (δ) (MeOH-d4, 200.15 MHz): 7.27 (d, J = 7.3 Hz, 1 H); 7.16-7.04 (m, 2 H); 4.29-3.82 (m, 7 H); 3.24-2.99 (m, 2 H); 2.67-2.67 (m, 2 H); 2.29 (s, 3 H); 2.25 (s, 3 H); 2.19-1.29 (m, 16 H); 0.93 (t, J = 7.5 Hz, 6 H).

Ion Electrospray Mass Spectrum M -2HCl +1: 497

Example 3

Preparation of (3S, 4aR, 6S, 8aR)-6-{[naphthalen-1-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.



A. Ehyl (3S, 4aR, 6S, 8aR)-6-{[(naphthalen-1-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

To a solution of 731 mg (1.79 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-(iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (may be prepared by the procedure described in Ornstein, et al., *Journal of Organic Chemistry*, 1994, 59, 7862-7869) in dry dimethylformamide (7 mL) at room temperature is added 1-naphthalenemethylamine (0.525 mL, 3.58 mmol) and potassium carbonate (743 mg, 5.37 mmol. The reaction mixture is allowed to stir at 90 °C overnight. The mixture is cooled to room temperature and treated with water (20 mL) and ethyl acetate. The layers are separated and the aqueous phase is extracted with ethyl acetate. The combined organic phases are dried over magnesium sulfate, filtered and concentrated to dryness. The resulting residue is purified by radial silica gel chromatography (chromatroton 4000 micron plate, hexane-ethyl acetate 1:1) to provide 471 mg (60% yield) of the title compound as a yellow oil.

Ion Electrospray Mass Spectrum M+1 : 439

B. Ethyl (3S, 4aR, 6S, 8aR)-6-[(cyanomethyl-naphthalen-1-ylmethyl-amino)-methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

To a solution of 281 mg (0.64 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(naphthalen-1-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 3A) in acetonitrile (6 mL) at room temperature is added bromoacetonitrile (0.223 mL, 3.20 mmol) and sodium bicarbonate (135 mg, 1.34 mmol). The reaction mixture is stirred at 80 °C overnight, cooled to room temperature and concentrated to dryness. The resulting residue is purified by radial

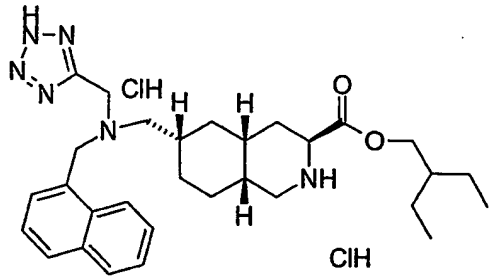
chromatography (chromatroton, 2000 micron plate, hexane-ethyl acetate 7:3) to afford 246 mg (80% yield) of the title compound as a colorless foam.
Ion Electrospray Mass Spectrum M+1 : 478

C. 3S, 4aR, 6S, 8aR)-6-{[Naphthalen-1-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.

A mixture of 355 mg (0.42 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-[(cyanomethyl-naphthalen-1-ylmethyl-amino)-methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 3B) and azido-tri-n-butylstannane (0.230 mL, 0.84 mmol) is heated at 100 °C for 4 days. The reaction is cooled to room temperature and 1N hydrochloric acid (10 mL) and ethyl acetate are added. After stirring 15 min., the layers are separated and the aqueous phase is extracted with ethyl acetate. The organic phase is dried over magnesium sulfate, filtered and concentrated to dryness. To the resulting residue is added 5N hydrochloric acid (7 mL) and the mixture is heated at 100 °C overnight. The reaction is cooled to room temperature and concentrated to dryness. The crude reaction product is purified by ion exchange chromatography (Strong Cation Exchange, 2M ammonia in methyl alcohol) to provide 127 mg (70% yield) of the title compound as a white solid.
1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 8.24-8.20 (m, 1 H); 8.09-7.98 (m, 2 H); 7.73-7.55 (m, 4 H); 5.11 (s, 2 H); 3.97-3.90 (m, 1 H); 3.21-2.97 (m, 4 H); 2.06-0.87 (m, 11 H).
Ion Electrospray Mass Spectrum M+1 : 435

Example 4

Preparation of 2-ethylbutyl (3S, 4aR, 6S, 8aR)-6-{[(naphthalen-1-ylmethyl-1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.



The title compound is prepared by reacting (3S, 4aR, 6S, 8aR)-6-{[naphthalen-1-ylmethyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid 960 mg (1.88 mmol) (Example 3) with 1.51 mL (20.72 mmol) of thionyl chloride in 5 mL of 2-ethyl butanol according to the procedure of Example 2.

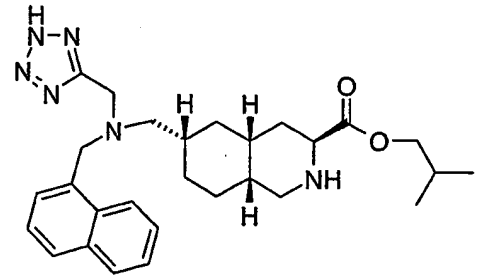
800 mg (72% yield)

1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 8.21 (d, J = 8.3 Hz, 1 H); 8.09-7.95 (m, 3 H); 7.69-7.58 (m, 3 H); 5.04 (s, 2 H); 4.86 (s, 2 H); 4.23-4.01 (m, 3 H); 3.25-2.90 (m, 4 H); 2.20-1.99 (m, 16 H); 0.93 (t, J=7.5 Hz, 6 H).

Ion Electrospray Mass Spectrum M -2HCl +1 : 519

Example 5

Preparation of isobutyl (3S, 4aR, 6S, 8aR)-6-{[naphthalen-1-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.



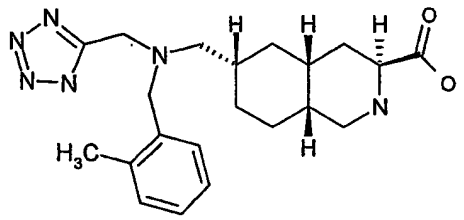
To 2.99 g (5.86 mmol) of (3S, 4aR, 6S, 8aR)-6-{[Naphthalen-1-ylmethyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (Example 3) at room temperature is added a saturated solution of

hydrogen chloride gas in isobutyl alcohol (5.4 mL). The reaction mixture is allowed to stir at 95 °C overnight. The reaction is cooled to room temperature and concentrated to dryness. The crude reaction product is purified by flash chromatography (ethyl acetate-methanol 3:1) to afford 943 mg (33% yield) of the title compound.

Ion Electrospray Mass Spectrum M+1 : 491

Example 6

Preparation of (3S, 4aR, 6S, 8aR)-6-{[2-methyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.



A. Ehyl (3S, 4aR, 6S, 8aR)-6-(2-methyl-benzylamino-methyl)-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 811 mg (1.98 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-(iodomethyl)-2 (methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate with 0.491 mL (3.96 mmol) of 2-methylbenzylamine and 822 mg (5.94 mmol) of potassium carbonate in 8 mL of dimethylformamide according to the procedure of Example 3A.

A yellow oil (385 mg, 48% yield) is obtained.

Ion Electrospray Mass Spectrum M+1 : 403

B. thyl (3S, 4aR, 6S, 8aR)-6-{[(cyanomethyl-(2-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 335 mg (0.83 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-(2-methyl-benzylamino-methyl)-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 6A) with 0.249 mL (4.15 mmol) of bromoacetonitrile and 175 mg (1.74 mmol) of sodium bicarbonate according to the procedure of Example 3B.

A colorless oil (310 mg, 84% yield) is obtained.

Ion Electrospray Mass Spectrum M+1 : 442

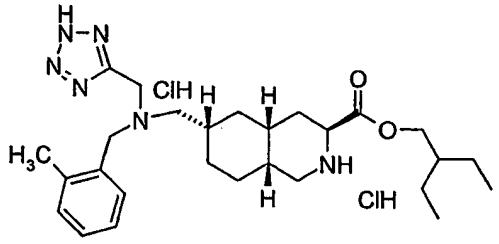
C. 3S, 4aR, 6S, 8aR)-6-{[2-Methyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid

The title compound is prepared by reacting 302 mg (0.68 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(cyanomethyl-(2-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 6B) with 0.373 mL (1.36 mmol) of azido-tri-n-butylstannane according to the procedure of Example 3C. The reaction product is treated with 11 mL of 5N hydrochloric acid to afford 145 mg (54% yield) of the title compound as a white solid.

Analysis calculated for $C_{21}H_{30}N_6O_2.1$ MeOH.0.2 H_2O: % C, 60.87; % H, 7.99; % N, 19.36. Found: % C, 61.12; % H, 7.79; % N, 18.75.

Example 7

Preparation of 2-ethylbutyl (3S, 4aR, 6S, 8aR)-6-{[2-methyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.

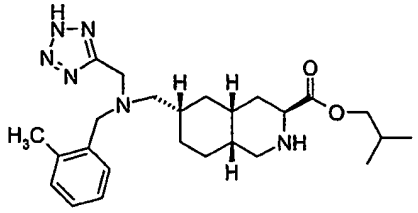


To (3S, 4aR, 6S, 8aR)-6-{[2-methyl-benzyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (Example 6) (1.18 g, 2.12 mmol) at room temperature is added a saturated solution of hydrogen chloride gas in 2-ethylbutyl alcohol (50 mL). The reaction mixture is stirred at 120 °C for two days, cooled to room temperature and concentrated to dryness. The resulting residue is washed with ether and ethyl acetate to give the title compound 1.09 g (78% yield) as a white solid. 1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.54-7.51 (m, 1 H); 7.34-7.27 (m, 4 H); 4.48 (s, 2 H); 4.30-4.00 (m, 5 H); 3.21-2.85 (m, 4 H); 2.38 (s, 3 H); 2.22-1.19 (m, 16 H); 0.94 (t, J = 7.5 Hz, 6 H).

Ion Electrospray Mass Spectrum M –2HCl +1 : 483

Example 8

Preparation of isobutyl (3S, 4aR, 6S, 8aR)-6-{[2-methyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate



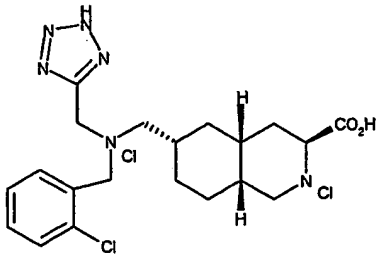
The title compound is prepared by reacting 2.29 g (5.74 mmol) of (3S, 4aR, 6S, 8aR)-6-{[2-methyl-benzyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (Example 6) with 4.2 mL of a saturated solution of hydrogen chloride in isobutyl alcohol according to the procedure of Example 5.

1.96 g (75% yield)

Ion Electrospray Mass Spectrum M+1 : 555

Example 9

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(2-chlorobenzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ehyl (3S, 4aR, 6S, 8aR)-6-{[(2-chlorobenzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 237 mg (0.62 mmol) ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 174 mg (1.24 mmol) of 2-chlorobenzaldehyde, 367 mg (1.74 mmol) of sodium triacetoxyborohydride and 0.219 mL (3.73 mmol) of acetic acid according to the procedure of Example 1A.

163 mg (52% yield)

Ion Electrospray Mass Spectrum M+1 : 506

B. (3S, 4aR, 6S, 8aR)-6-{[(2-Chlorobenzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 200 mg (0.39 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(2-chlorobenzyl)-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 9A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

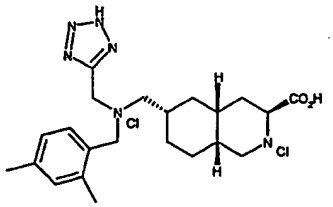
153 mg (80% yield)

1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.71-7.71 (m, 1 H); 7.36-7.30 (m, 3 H); 4.85 (s, 2 H); 4.61 (s, 2 H); 4.02 (d, J = 10.5 Hz, 1 H); 3.11-3.06 (m, 4 H); 2.18-1.66 (m, 10 H); 1.16-1.15 (m, 1 H).

Ion Electrospray Mass Spectrum M –2HCl +1: 419

Example 10

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(2,4-dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,4-dimethyl-benzyl)-1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 1.0 g (4.47 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 1.3 mL (8.94 mmol) of 2,4-dimethylbenzaldehyde, 2.7 g (12.79 mmol) of sodium triacetoxyborohydride and 1.6 mL (19.98 mmol) of acetic acid according to the procedure of Example 1A.

1.71g (77% yield)

Ion Electrospray Mass Spectrum M+1 : 498

B. (3S, 4aR, 6S, 8aR)-6-{[(2,4-Dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 1.2 g (2.40 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,4-dimethyl-benzyl)-1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 10A) with 20 mL of 3N hydrochloric acid according to the procedure of Example 1B.

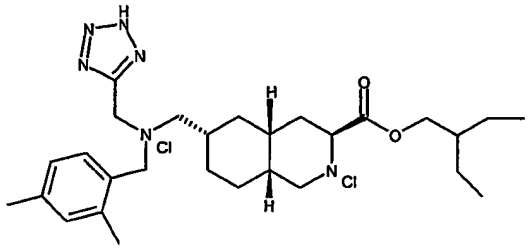
874 mg (75% yield)

1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.59 (d, J = 8.1 Hz, 1 H); 7.16 (d, J = 6.2 Hz, 2 H); 4.56 (s, 2 H); 4.02-3.94 (m, 1 H); 3.26-3.03 (m, 4 H); 2.38 (s, 3 H); 2.34 (s, 3 H); 2.14-1.91 (m, 6 H); 1.83-1.50 (m, 6 H); 1.07-0.98 (m, 1 H).

Ion Electrospray Mass Spectrum M –2HCl +1: 413

Example 11

Preparation of 2-ethylbutyl (3S, 4aR, 6S, 8aR)-6-{[(2,4-dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.



The title compound is prepared by reacting 700 mg (1.44 mmol) of (3S, 4aR, 6S, 8aR)-6-{[(2,4-dimethyl-benzyl)-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride (Example 10) with 1.1 mL (14.4 mmol) of thionyl chloride in 5 mL of 2-ethyl butanol according to the procedure of Example 2.

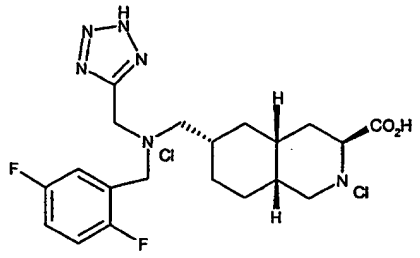
558 mg (68% yield)

1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.53 (d, J = 8.3 Hz, 1 H); 7.13 (d, J = 6.7 Hz, 2 H); 4.72 (s, 2 H); 4.43 (s, 2 H); 4.29-4.04 (m, 3 H); 3.20-3.02 (m, 3 H); 2.36 (s, 3 H); 2.33 (s, 3 H); 2.19-1.91 (m, 7 H); 1.83-1.24 (m, 11 H); 0.96-0.89 (m, 6 H).

Ion Electrospray Mass Spectrum M –2HCl +1: 497

Example 12

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(2,5-difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,5-difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 200 mg (0.52 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 149 mg (1.05 mmol) of 2,5-difluorobenzaldehyde, 307 mg (1.45 mmol) of sodium triacetoxyborohydride and 0.250 mL (3.12 mmol) of acetic acid according to the procedure of Example 1A.

137 mg (52% yield)

Ion Electrospray Mass Spectrum M+1 : 507

B. (3S, 4aR, 6S, 8aR)-6-{[(2,5-Difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 160 mg (0.28 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,5-difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 12A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

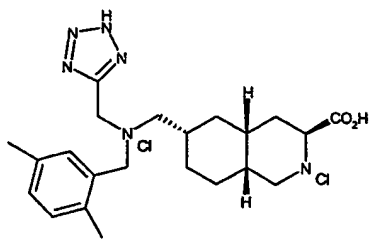
99 mg (72% yield)

1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.71-7.71 (m, 1 H); 7.36-7.30 (m, 3 H); 4.85 (s, 2 H); 4.61 (s, 2 H); 4.04 (d, J = 10.5 Hz, 1 H); 3.11-3.06 (m, 4 H); 2.18-1.66 (m, 10 H); 1.16-1.15 (m, 1 H).

Ion Electrospray Mass Spectrum M -2HCl +1 : 421

Example 13

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(2,5-Dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,5-dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 1.0 g (4.47 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 1.3 mL (8.94 mmol) of 2,5-dimetylbenzaldehyde, 2.7 g (12.79 mmol) of sodium triacetoxyborohydride and 1.6 mL (19.98 mmol) of acetic acid according to the procedure of Example 1A.

1.73g (78% yield)

Ion Electrospray Mass Spectrum M+1 : 498

B. (3S, 4aR, 6S, 8aR)-6-{[(2,5-Dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

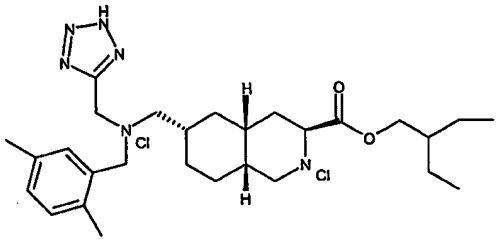
The title compound is prepared by reacting 1.1 g (2.20 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,5-dimethyl-benzyl)-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2 (methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 13A) with 20 mL of 3N hydrochloric acid according to the procedure of Example 1B.

930 mg (87% yield)

Analysis calculated for $C_{23}H_{32}N_6O_2.2\ HCl.2.10\ H_2O$: %C, 51.60; %H, 7.19; %N, 15.70. Found: C, 51.60; %H, 7.65; %N, 15.59

Example 14

Preparation of 2-ethylbutyl (3S, 4aR, 6S, 8aR)-6-{[(2,5-dimethyl-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.



The title compound is prepared by reacting 1.1 g (2.26 mmol) of (3S, 4aR, 6S, 8aR)-6-{[(2,5-dimethyl-benzyl)-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride (Example 13) with 1.82 mL (24.92 mmol) of thionyl chloride in 5 mL of 2-ethyl butanol according to the procedure of Example 2.

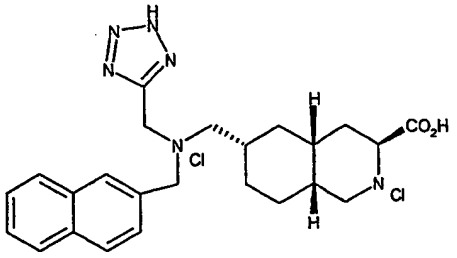
1.00 g (78% yield)

Analysis calculated for $C_{28}H_{44}N_6O_2.2\ HCl.0.41\ H_2O$: %C, 58.28; %H, 8.18 ; %N, 14.56.

Found: C, 58.28; %H, 7.99; %N, 13.98

Example 15

Preparation of (3S, 4aR, 6S, 8aR)-6-{[naphthalen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[naphthalen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 320 mg (0.84 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 262 mg (1,68 mmol) of naphthalene-2-carbaldehyde, 495 mg (2.35 mmol) of sodium triacetoxyborohydride and 0.289 mL (5.05 mmol) of acetic acid according to the procedure of Example 1A.

218 mg (50% yield)

Ion Electrospray Mass Spectrum M+1 : 521

B. (3S, 4aR, 6S, 8aR)-6-{[Naphthalen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 150 mg (0.28 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[naphthalen-2-ylmethyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 15A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

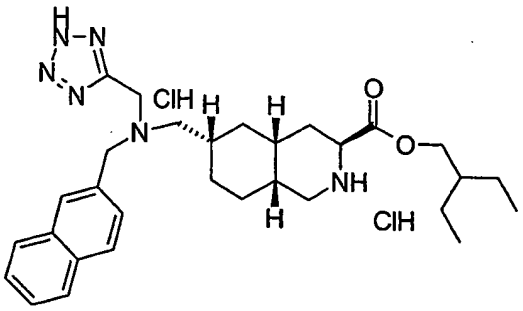
112 mg (79% yield)

Analysis calculated for $C_{24}H_{30}N_6O_2.2\ HCl.2.35\ H_2O$: %C, 52.42; %H, 6.73; %N, 15.28.

Found: C, 52.42; %H, 6.55; %N, 14.97.

Example 16

Preparation of 2-ethylbutyl(3S, 4aR, 6S, 8aR)-6-{[Naphthalen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.



The title compound is prepared by reacting 473 mg (0.93 mmol) of (3S, 4aR, 6S, 8aR)-6-{[naphthalen-2-ylmethyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride (Example 15) with 0.746 mL (10.23 mmol) of thionyl chloride in 21 mL of 2-ethyl butanol according to the procedure of Example 2.

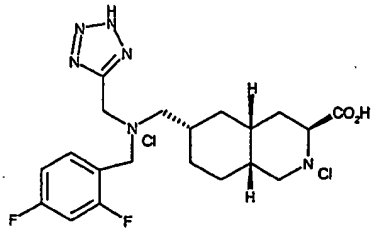
483 mg (85% yield)

1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 8.06 (s, 1 H); 7.97-7.88 (m, 3 H); 7.68 (d, J = 8.6 Hz, 1 H); 7.57-7.52 (m, 2 H); 4.54 (s, 2 H); 4.36 (s, 2 H); 4.25 (m, 3 H); 3.16-2.91 (m, 4 H); 2.10-1.29 (m, 16 H); 0.93 (t, J = 7.5 Hz, 6 H).

Ion Electrospray Mass Spectrum M -2HCl + 1: 519

Example 17

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(2,4-Difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,4-difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 200 mg (0.52 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 149 mg (1.05 mmol) of 2,4-difluorbenzaldehyde, 307 mg (1.45 mmol) of sodium triacetoxyborohydride and 0.250 mL (3.12 mmol) of acetic acid according to the procedure of Example 1A.

137 mg (52% yield)

Ion Electrospray Mass Spectrum M+1 : 507

B. (3S, 4aR, 6S, 8aR)-6-{[(2,4-Difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 130 mg (0.22 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,4-difluoro-benzyl)-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 17A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

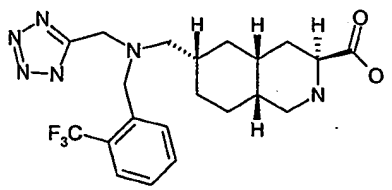
77 mg (71% yield)

^{1}H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.94-7.87 (m, 1 H); 7.21-7.11 (m, 3 H); 4.81 (s, 2 H); 4.59 (s, 2 H); 4.06-3.95 (m, 1 H); 3.29-3.05 (m, 4 H); 2.15-1.53 (m, 10 H); 1.13-1.13 (m, 1 H).

Ion Electrospray Mass Spectrum M –2HCl +1: 421

Example 18

Preparation of (3S, 4aR, 6S, 8aR)-6-{[2-trifluoromethyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(2-trifluromethyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 1.00 g (2.44 mmol) of ethyl (3S, 4aR, 6S,8aR)-6-(iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate with 0.684 mL (4.88 mmol) of 2-trifluoromethylbenzylamine and 1.01 g (7.32 mmol) of potassium carbonate in 10 mL of dimethylformamide according to the procedure of Example 3A.

496 mg (44% yield)

Ion Electrospray Mass Spectrum M+1 : 457

B. Ethyl (3S, 4aR, 6S, 8aR)-6-[(cyanomethyl-2-trifluoromethyl-benzyl-amino)-methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 400 mg (0.88 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(2-trifluromethyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate(Example 18A) with 0.306 mL (4.40 mmol) of bromoacetonitrile and 185 mg (1.85 mmol) of sodium bicarbonate in 8.7 mL of acetonitrile according to the procedure of Example 3B.

430 mg (99% yield) of a colorless oil

Ion Electrospray Mass Spectrum M+1 : 496

C. (3S, 4aR, 6S, 8aR)-6-{[2-Trifluoromethyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-decahydroisoquinoline-3-carboxylic acid.

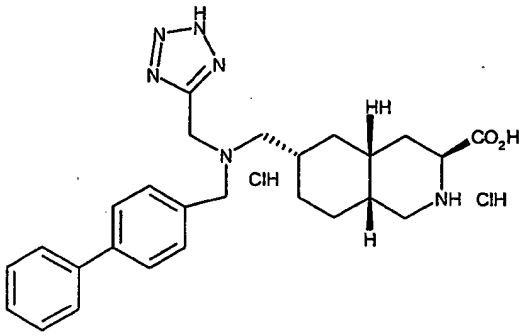
The title compound is prepared by reacting 355 mg (0.72 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-[(cyanomethyl-2-trifluoromethyl-benzyl-amino)-methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 18B) with 0.478 mL (1.44 mmol) of azido-tri-n-butylstannane and, subsequently, 12 mL of 5N hydrochloric acid according to the procedure of Example 3C.

A white solid (162 mg, 50% yield) is obtained.

Analysis calculated for $C_{21}H_{27}F_3N_6O_2.0.5\ H_2O$: % C, 54.66; % H, 6.12; % N, 18.21. Found: % C, 55.19; % H, 6.05; % N, 17.70.

Example 19

Preparation of (3S, 4aR, 6S, 8aR)-6-{[biphenyl-4-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[biphenyl-4-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 200 mg (0.52 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 191 mg (1.05 mmol) of biphenyl-4-carbaldehyde, 307 mg (1.45 mmol) of sodium triacetoxyborohydride and 0.250 mL (3.12 mmol) of acetic acid according to the procedure of Example 1A.

184 mg (65% yield)

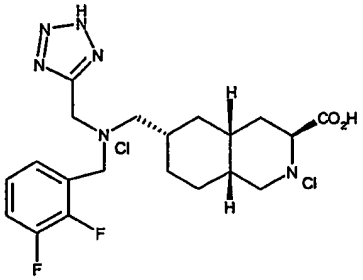
Ion Electrospray Mass Spectrum M+1 : 547

B. (3S, 4aR, 6S, 8aR)-6-{[Biphenyl-4-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 100 mg (0.18 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[biphenyl-4-ylmethyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 19A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.
50 mg (52% yield)
1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.77-7.77 (m, 5 H); 7.66 (dd, J = 8.3, 1.6 Hz, 2 H); 7.51-7.37 (m, 2 H); 4.84 (s, 2 H); 4.57 (s, 2 H); 4.00 (d, J = 12.1 Hz, 1 H); 3.24-3.01 (m, 4 H); 2.14-1.98 (m, 10 H); 1.12-1.06 (m, 1 H).
Ion Electrospray Mass Spectrum M –2HCl +1: 461

Example 20

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(2,3-difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,3-difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 200 mg (0.52 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 149 mg (1.05 mmol) of 2,3-difluorbenzaldehyde, 307 mg (1.45 mmol) of sodium

triacetoxyborohydride and 0.250 mL (3.12 mmol) of acetic acid according to the procedure of Example 1A.

105 mg (40% yield)

Ion Electrospray Mass Spectrum M+1 : 507

B. (3S, 4aR, 6S, 8aR)-6-{[(2,3-Difluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 100 mg (0.20 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(2,3-difluoro-benzyl)-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 20A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

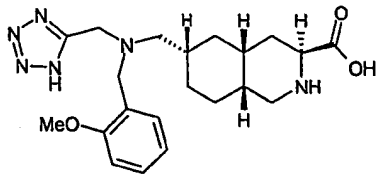
69 mg (70% yield)

1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.71-7.33 (m, 4 H); 4.84 (s, 2 H); 4.66 (s, 2 H); 4.04 (d, J = 10.7 Hz, 1 H); 3.12-3.06 (m, 2 H); 2.15-1.66 (m, 10 H); 1.16-1.16 (m, 1 H).

Ion Electrospray Mass Spectrum M –2HCl +1: 421

Example 21

Preparation of (3S, 4aR, 6S, 8aR)-6-{[2-methoxy-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(2-methoxy-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 1.00 g (2.44 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-(iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-

decahydroisoquinoline-3-carboxylate with 0.673 mL (4.88 mmol) of 2-methoxybenzylamine and 1.01 g (7.32 mmol) of potassium carbonate in 10 mL of dimethylformamide according to the procedure of Example 3A.
A yellow oil (698 mg, 68% yield) is obtained.
Ion Electrospray Mass Spectrum M+1 : 419

B. Ethyl (3S, 4aR, 6S, 8aR)-6-{[cyanomethyl-(2-methoxy-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

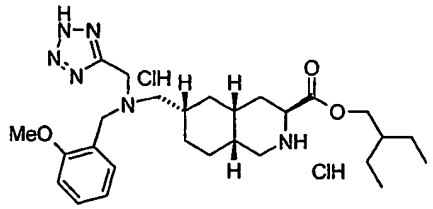
The title compound is prepared by reacting 600 mg (1.43 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(2-methoxy-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 21A) with 0.498 mL (7.15 mmol) of bromoacetonitrile and 301 mg (3.00 mmol) of sodium bicarbonate in 14.2 mL of acetonitrile according to the procedure of Example 3B. A colorless oil (369 mg, 56% yield) is obtained.
Ion Electrospray Mass Spectrum M+1 : 458

C. (3S, 4aR, 6S, 8aR)-6-{[2-Methoxy-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.

The title compound is prepared by reacting 294 mg (0.64 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[cyanomethyl-(2-methoxy-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 21B) with 0.351 mL (1.28 mmol) of azido-tri-n-butylstannane and, subsequently, 10 mL of 5N hydrochloric acid according to the procedure of Example 3C.
A white solid (112 mg, 42% yield) is obtained.
Analysis calculated for $C_{21}H_{30}N_6O_3$.0.7 MeOH: % C, 59.65; % H, 7.57; % N, 19.23.
Found: % C, 60.02; % H, 7.32; % N, 18.67.

Example 22

Preparation of 2-ethylbutyl (3S, 4aR, 6S, 8aR)-6-{[2-methoxy-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.



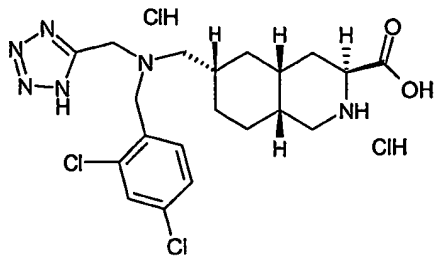
The title compound is prepared by reacting 500 mg (1.03 mmol) of (3S, 4aR, 6S, 8aR)-6-{[2-methoxy-benzyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (Example 21) with 0.827 mL (11.33 mmol) of thionyl chloride in 20 mL of 2-ethylbutyl alcohol according to the procedure of Example 2.

A white solid (548 mg, 93% yield) is obtained.

Analysis calculated for $C_{27}H_{42}N_6O_3.2HCl.1$ MeOH: % C, 55.72; % H, 8.01; % N, 13.92. Found: % C, 56.07; % H, 7.62; % N, 13.68.

Example 23

Preparation of (3S, 4aR, 6S, 8aR)-6-{[2,4-dichloro-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[2,4-dichloro-benzyl-(1*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate

The title compound is prepared by reacting 150 mg (0.39 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 138 mg (0.79 mmol) of 2,4-dichlorobenzaldehyde, 248 mg (1.17 mmol) of sodium triacetoxyborohydride and 0.134 mL (2.34 mmol) of acetic acid in 1.7 mL of 1,2-dichloroethane according to the procedure of Example 1A. A colorless oil (73 mg, 35% yield) is obtained.

Ion Electrospray Mass Spectrum M+1 : 539

B. (3S, 4aR, 6S, 8aR)-6-{[2,4-Dichloro-benzyl-(1*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

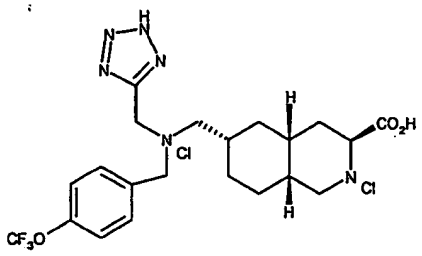
The title compound is prepared by reacting 73 mg (0.14 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[2,4-dichloro-benzyl-(1H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 23A) with 3.0 mL of 3N hydrochloric acid according to the procedure Example 1B.

A white solid (46 mg, 48% yield) is obtained.

Analysis calculated for $C_{20}H_{26}Cl_2N_6O_2.3HCl.0.5MeOH$: % C, 42.54; % H, 5.40; % N, 14.52. Found: % C, 42.77; % H, 5.00; % N, 14.26.

Example 24

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-(4-trifluoromethoxy-benzyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3*S*, 4a*R*, 6*S*, 8a*R*)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-(4-trifluoromethoxy-benzyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 200 mg (0.52 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 199 mg (1.05 mmol) of 3-trifluoromethoxy-benzaldehyde, 307 mg (1.45 mmol) of sodium triacetoxyborohydride and 0.250 mL (3.12 mmol) of acetic acid according to the procedure of Example 1A.

A yield of 181 mg (63%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 555

B. (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-Tetrazol-5-ylmethyl)-(4-trifluoromethoxy-benzyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound was prepared by reacting 100 mg (0.18 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-(4-trifluoromethoxy-benzyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 24A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

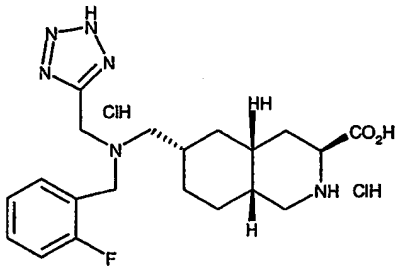
A yield of 73 mg (75%) is obtained.

1H-NMR (δ) (MeOH-d4, 200.15 MHz): 7.78-7.77 (m, 2 H); 7.42-7.39 (m, 2 H); 4.80 (s, 2 H); 4.48-4.48 (m, 2 H); 4.01-3.95 (m, 1 H); 3.17-3.04 (m, 4 H); 2.14-1.61 (m, 10 H).

Ion Electrospray Mass Spectrum M –2HCl +1: 469

Example 25

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(2-fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(2-fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 300 mg (0.74 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 165 mg (1,57 mmol) of 2-fluorobenzaldehyde, 463 mg (2.19 mmol) of sodium triacetoxyborohydride and 0.270 mL (4.70 mmol) of acetic acid according to the procedure of Example 1A.

A yield of 170 mg (47%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 489

B. (3S, 4aR, 6S, 8aR)-6-{[(2-Fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

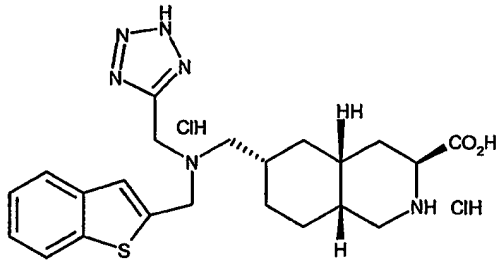
The title compound is prepared by reacting 180 mg (0.36 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(2-fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(metho xycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 25A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

A yield of 150 mg (88%) is obtained.

Analysis calculated for $C_{20}H_{27}FN_6O_2.4.48$ HCl: %C, 42.45; %H, 5.61; %N, 14.85. Found: C, 42.45; %H, 6.10; %N, 14.56

Example 26

Preparation of (3S, 4aR, 6S, 8aR)-6-{[benzo[*b*]thiophen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[benzo[b]thiophen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 250 mg (0.67 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 212 mg (1.314 mmol) of benzo[b]thiophen-2-carbaldehyde, 416 mg (1.97 mmol) of sodium triacetoxyborohydride and 0.220 mL (3.92 mmol) of acetic acid according to the procedure of Example 1A.

A yield of 264 mg (75%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 527

B. (3S, 4aR, 6S, 8aR)-6-{[Benzo[*b*]thiophen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 100 mg (0.19 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[benzo[b]thiophen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-

2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 26A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

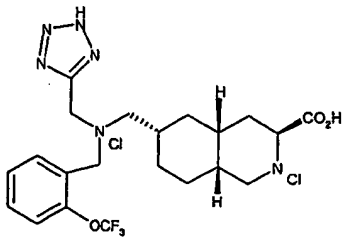
A yield of 385 mg (75%) is obtained.

1H-NMR (δ) (MeOH-d4, 200.15 MHz): 7.91-7.81 (m, 3 H); 7.45-7.41 (m, 2 H); 4.92-4.92 (m, 4 H); 3.98 (d, J = 13.7 Hz, 1 H); 3.15-2.95 (m, 2 H); 2.14-1.98 (m, 6 H); 1.84-1.55 (m, 6 H); 1.19-1.00 (m, 1 H).

Ion Electrospray Mass Spectrum M –2HCl +1: 441

Example 27

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-(2-trifluoromethoxy-benzyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-(2-trifluoromethoxy-benzyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 200 mg (0.52 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 199 mg (1.05 mmol) of 2-trifluoromethoxy-benzaldehyde, 307 mg (1.45 mmol) of sodium triacetoxyborohydride and 0.250 mL (3.12 mmol) of acetic acid according to the procedure of Example 1A.

A yield of 152 mg (53%) is obtained.

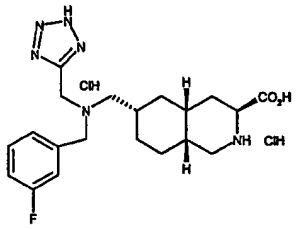
Ion Electrospray Mass Spectrum M+1 : 555

B. (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-Tetrazol-5-ylmethyl)-(2-trifluoromethoxy-benzyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 100 mg (0.18 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-(2-trifluoromethoxy-benzyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 27A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.
A yield of 73 mg (75%) is obtained.
Analysis calculated for $C_{21}H_{27}F_3N_6O_2.2$ HCl.3.11 H_2O: %C, 43.38; %H, 6.11; %N, 14.45.
Found: C, 43.38; %H, 5.55; %N, 15.59

Example 28

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(3-fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(3-fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 300 mg (0.74 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 165 mg (1.57 mmol) of 3-fluorobenzaldehyde, 463 mg (2.19 mmol) of sodium triacetoxyborohydride and 0.270 mL (4.70 mmol) of acetic acid according to the procedure of Example 1A.

A yield of 144 mg (40%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 489

B. (3S, 4aR, 6S, 8aR)-6-{[(3-Fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

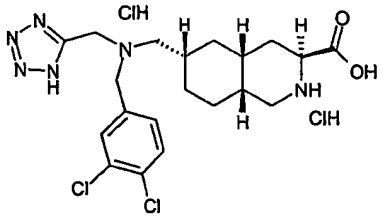
The title compound is prepared by reacting 150 mg (0.30 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(3-fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 28A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

A yield of 107 mg (75%) is obtained.

Analysis calculated for $C_{20}H_{27}FN_6O_2.4.0$ HCl: %C, 43.70; %H, 5.69; %N, 15.29. Found: %C, 43.87; %H, 6.09; %N, 14.89

Example 29

Preparation of (3S, 4aR, 6S, 8aR)-6-{[3,4-dichloro-benzyl-(1*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[3,4-dichloro-benzyl-(1*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 150 mg (0.39 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 138 mg (0.79 mmol) of 3,4-dichlorobenzaldehyde, 248 mg (1.17 mmol) of sodium triacetoxyborohydride and 134 mg (2.34 mmol) of acetic acid in 1.7 mL of 1,2-

dichloroethane according to the procedure of Example 1A. A colorless oil (97 mg, 46% yield) is obtained.

Ion Electrospray Mass Spectrum M+1 : 539

B. (3S, 4aR, 6S, 8aR)-6-{[3,4-Dichloro-benzyl-(1*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

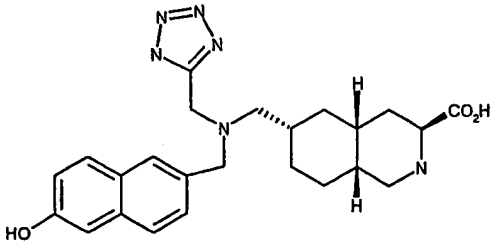
The title compound is prepared by reacting 97 mg (0.18 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[3,4-dichloro-benzyl-(1*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 29A) with 3.0 mL of 3N hydrochloric acid according to the procedure of Example 1B.

A white solid (52 mg, 55% yield) is obtained.

Analysis calculated for $C_{20}H_{26}Cl_2N_6O_2.3HCl$: % C, 42.69; % H, 5.19; % N, 14.93. Found: % C, 42.79; % H, 5.02; % N, 14.67.

Example 30

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(6-hydroxy-naphthalen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(6-methoxy-naphthalen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 150 mg (0.39 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 147 mg (0.79 mmol) of 6-methoxy-2-naphthaldehyde, 248 mg (1.17 mmol) of sodium triacetoxyborohydride and 0.134 mL (2.34 mmol) of acetic acid in 1.7 mL of 1,2-dichloroethane according to the procedure of Example 1A. A yellow oil (110 mg, 51% yield) is obtained.

Ion Electrospray Mass Spectrum M+1 : 551

B. (3S, 4aR, 6S, 8aR)-6-{[(6-Hydroxy-naphthalen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 110 mg (0.20 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(6-methoxy-naphthalen-2-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 30A) with 3.2 mL of 3N hydrochloric acid according to the procedure of Example 1B. The crude reaction product is purified by reverse phase solid phase extraction (C18 Cartridge) eluting with mixtures of water and methanol.

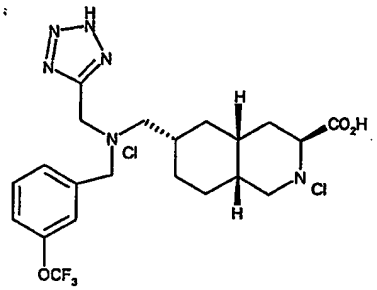
A pink solid (16 mg, 15% yield) is obtained.

1H-NMR (δ) (D_2O-KOD, 200.15 MHz): 7.45 (d, J = 8.6 Hz, 2 H); 7.37 (s, 1 H); 7.12 (d, J = 8.6 Hz, 1 H); 6.82 (d, J=8.3 Hz, 1 H); 6.71 (s, 1 H); 3.75 (s, 2 H); 3.46 (s, 2H); 2.90 (m, 1 H); 2.46-2.24 (m, 2 H); 2.05 (d, J = 5.9 Hz, 2 H); 1.54-0.81 (m, 11 H).

Ion Electrospray Mass Spectrum M+1 : 451

Example 31

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-(3-trifluoromethoxy-benzyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-(3-trifluoromethoxy-benzyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 200 mg (0.52 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 199 mg (1.05 mmol) of 3-trifluoromethoxy-benzaldehyde, 307 mg (1.45 mmol) of sodium triacetoxyborohydride and 0.250 mL (3.12 mmol) of acetic acid according to the procedure of Example 1A.

A yield of 158 mg (55%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 555

B. (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-Tetrazol-5-ylmethyl)-(3-trifluoromethoxy-benzyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 100 mg (0.18 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-(3-trifluoromethoxy-benzyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 31A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

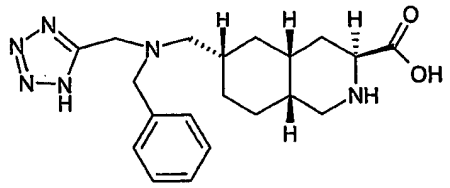
A yield of 72 mg (74%) id obtained.

Analysis calculated for $C_{26}H_{32}F_3N_6O_2.4.11$ HCl: %C, 41.87; %H, 5.21; %N, 13.95.

Found: C, 42.21; %H, 5.44; %N, 13.55

Example 32

Preparation of (3S, 4aR, 6S, 8aR)-6-{[benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-(benzylamino-methyl)-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 2.00 g (4.89 mmol) of ethyl (3S, 4aR, 6S,8aR)-6-(iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate) with 1.1 mL (9.78 mmol) of benzylamine and 2.00 g (14.67 mmol)of potassium carbonate in 20 mL of dimethylformamide according to the procedure of Example 3A.

A yellow oil 1.02 g (54%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 389

B. Ethyl (3S, 4aR, 6S, 8aR)-6-[(benzyl-cyanomethyl-amino)-methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 450 mg (1.16 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-(benzylamino-methyl)-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 32A) with 0.404 mL (5.80 mmol) of bromoacetonitrile and 244 mg (2.44 mmol) of sodium bicarbonate in 11 mL of acetonitrile according to the procedure of Example 3B.

A colorless oil 353 mg (71%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 428

C. (3S, 4aR, 6S, 8aR)-6-{[Benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

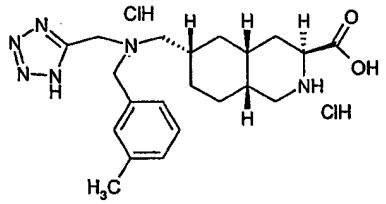
The title compound is prepared by reacting 214 mg (0.50 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-[(benzyl-cyanomethyl-amino)-methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 32B) with 0.274 mL (1.00 mmol) of azido-n-butylstannane and, subsequently, 5.3 mL of 6N hydrochloric acid according to the procedure of Example 3C.

A white solid 132 mg (69%) is obtained.

Analysis calculated for $C_{20}H_{28}N_6O_2.1H_2O.1MeOH$: % C, 58.05; % H, 7.89; % N, 19.34. Found: % C, 58.30; % H, 7.40; % N, 19.42.

Example 33

Preparation of (3S, 4aR, 6S, 8aR)-6-{[3-methyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(3-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 1.00 g (2.44 mmol)of ethyl (3S, 4aR, 6S, 8aR)-6-(iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate with 0.350 mL (2.79 mmol) of 3-methylbenzylamine and 1.01 g (7.32 mmol) of potassium carbonate in 10 mL of dimethylformamide according to the procedure of Example 3A.

A yellow oil (520 mg, 53%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 403

B. Ethyl (3S, 4aR, 6S, 8aR)-6-{[cyanomethyl-(3-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 502 mg (1.25 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(3-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 33A) with 0.435 mL (6.25 mmol) of bromoacetonitrile, and 364 mg (2.63 mmol) of potassium carbonate in 15 mL of acetonitrile according to the procedure of Example 3B. A yellow oil (316 mg, 57% yield) is obtained.

Ion Electrospray Mass Spectrum M+1 : 442

C. (3S, 4aR, 6S, 8aR)-6-{[3-Methyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

A mixture of 316 mg (0.72 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[cyanomethyl-(3-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyldecahydroisoquinoline-3-carboxylate (Example 33B) and azido-tri-n-butylstannane (0.592 mL, 2.16 mmol) in 0.7 mL of toluene is heated to 100 °C for 24 hours. After cooling to room temperature, 10 mL of 1N hydrochloric acid and 20 mL of ethyl acetate are added and the mixture is stirred at room temperature for 15 minutes. The layers are separated and the aqueous phase is extracted with ethyl acetate. The combined organic extracts are dried over magnesium sulfate, filtered and concentrated to dryness. To the resulting solid at room temperature is added 12 mL of 6N hydrochloric acid. The reaction mixture is heated at reflux overnight. The reaction mixture is cooled to room temperature and ether is added. The layers are separated and the aqueous phase is washed with ether and ethyl acetate. The aqueous phase is concentrated to dryness and the resulting solid is washed with ether and dried under vacuum to afford the title compound.

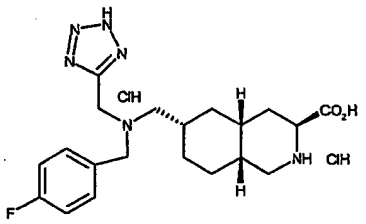
A yield of 192 mg (57%) is obtained.

Analysis calculated for $C_{21}H_{30}N_6O_2.2HCl.1.2H_2O$: % C, 51.16; % H, 7.03; % N, 17.05.

Found: % C, 50.97; % H, 6.46; % N, 17.46.

Example 34

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(4-fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(4-fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 300 mg (0.74 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 165 mg (1,57 mmol) of 4-fluorobenzaldehyde, 463 mg (2.19 mmol) of sodium triacetoxyborohydride and 0.270 mL (4.70 mmol) of acetic acid according to the procedure of Example 1A.

A yield of 152 mg (42%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 489

B. (3S, 4aR, 6S, 8aR)-6-{[(4-Fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

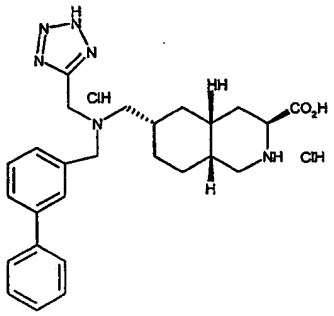
The title compound is prepared by reacting 130 mg (0.26 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(4-fluoro-benzyl)-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 34A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B.

A yield of 89 mg (72%) is obtained.

Analysis calculated for $C_{20}H_{27}FN_6O_2$.4.7 HCl: %C, 41.63; %H, 5.55; %N, 14.56. Found: C, 41.63; %H, 5.99; %N, 14.06

Example 35

Preparation of (3S, 4aR, 6S, 8aR)-6-{[biphenyl-3-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[biphenyl-3-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 200 mg (0.52 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 2) with 191 mg (1.05 mmol) of biphenyl-3-carbaldehyde, 307 mg (1.45 mmol) of sodium triacetoxyborohydride and 0.250 mL (3.12 mmol) of acetic acid according to the procedure of Example 1A.

A yield of 204 mg (72%) is obtained.

Ion Electrospray Mass Spectrum M+1 : 547

B. (3S, 4aR, 6S, 8aR)-6-{[Biphenyl-3-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

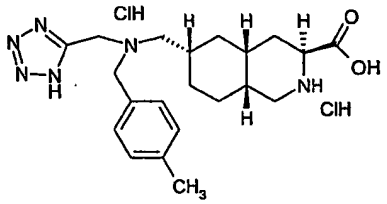
The title compound is prepared by reacting 150 mg (0.27 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[biphenyl-3-ylmethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 35A) with 6 mL of 6N hydrochloric acid according to the procedure of Example 1B. A yield of 92 mg (64%) is obtained.

1H-NMR (δ) (MeOH-d4, 200.15 MHz): 8.03 (s, 1 H); 7.79-7.29 (m, 8 H); 4.85 (s, 2 H); 4.62 (s, 2 H); 4.02-3.96 (m, 1 H); 3.07-2.80 (m, 2 H); 2.06-1.69 (m, 12 H); 1.16-1.09 (m, 1 H).

Ion Electrospray Mass Spectrum M –2HCl +1: 461

Example 36

Preparation of (3S, 4aR, 6S, 8aR)-6-{[4-methyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(4-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 1.00 g (2.44 mmol) of ethyl (3S, 4aR, 6S,8aR)-6-(iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate with 0.621 mL (4.88 mmol) of 4-methylbenzylamine and 1.01 g (7.32 mmol) of potassium carbonate in 10 mL of dimethylformamide according to the procedure of Example 3A.

A yellow oil (560 mg, 57%) is obtained.
Ion Electrospray Mass Spectrum M+1: 403

B. Ethyl (3S, 4aR, 6S, 8aR)-6-{[cyanomethyl-(4-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

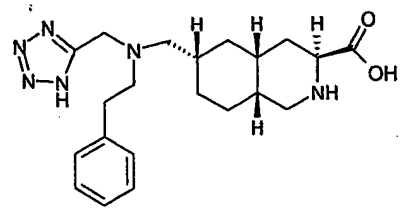
The title compound is prepared by reacting 494 mg (1.22 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(4-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 36A) with 0.425 mL (6.10 mmol) of bromoacetonitrile and 354 mg (2.56 mmol) of potassium carbonate in 15 mL of acetonitrile according to the procedure of Example 3B. 417 mg (78% yield) of a yellow oil is obtained.
Ion Electrospray Mass Spectrum M+1 : 442

C. (3S, 4aR, 6S, 8aR)-6-{[4-Methyl-benzyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride.

The title compound is prepared by reacting 417 mg of ethyl (3S, 4aR, 6S, 8aR)-6-{[cyanomethyl-(4-methyl-benzyl)-amino]-methyl}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 36B) with 0.773 mL of azido-tri-n-butylstannane in 0.9 mL of toluene and, subsequently, 16 mL of 6N hydrochloric acid according to the procedure of Example 3C.
A white solid (235 mg, 53% yield) is obtained.
Analysis calculated for $C_{21}H_{30}N_6O_2.2.7HCl$: % C, 50.76; % H, 6.63; % N, 16.91. Found: % C, 50.50; % H, 6.53; % N, 16.83.

Example 37

Preparation of (3S, 4aR, 6S, 8aR)-6-{[phenethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-(phenethylamino-methyl)-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 695 mg (1.70 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-(iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate with 0.427 mL (3.40 mmol) of phenethylamine and 706 mg (5.10 mmol) of potassium carbonate in 7 mL of dimethylformamide according to the procedure of Example 3A.

A yellow oil (362 mg, 53% yield) is obtained.

Ion Electrospray Mass Spectrum M+1 : 403

B. Ethyl (3S, 4aR, 6S, 8aR)-6-[(cyanomethyl-phenethyl-amino)-methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared by reacting 312 mg (0.78 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-(phenethylamino-methyl)-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 37A) with 0.272 mL (3.90 mmol) of bromoacetonitrile, and 164 mg (1.64 mmol) of sodium bicarbonate in 7.4 mL of acetonitrile according to the procedure of Example 3B. A colorless oil (232 mg, 68% yield) is obtained.

Ion Electrospray Mass Spectrum M+1: 442

C. (3S, 4aR, 6S, 8aR)-6-{[Phenethyl-(1(2)*H*-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.

The title compound is prepared by reacting 223 mg (0.51 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-[(cyanomethyl-phenethyl-amino)-methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 37B) with 0.280 mL

(1.02 mmol) of azido-tri-n-butylstannane and, subsequently, 8.3 mL of 5N hydrochloric acid according to the procedure of Example 3C.

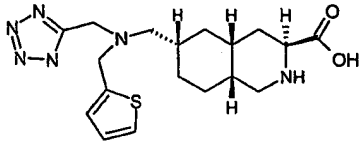
A white solid (135 mg, 77% yield) is obtained.

1H-NMR (δ) (MeOH-d4, 200.15 MHz): 7.32-7.19 (m, 5 H); 4.33 (s, 2 H); 3.63-3.52 (m, 1 H); 3.21-2.90 (m, 6 H); 2.74 (d, J = 6.5 Hz, 2 H); 2.14-1.10 (m, 11 H).

Ion Electrospray Mass Spectrum M+1 : 399

Example 38

Preparation of (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-tetrazol-5-ylmethyl)-thiophen-2-ylmethyl-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.



A. Ethyl (3S, 4aR, 6S, 8aR)-6-azidomethyl-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate:

To a solution of ethyl (3S, 4aR, 6S, 8aR)-6-*p*-toluene-sulfonyloxymethyl-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Preparation 3)(WO 0101972) (7.4 g, 16.3 mmol) in dimethylformamide (80 mL) at room temperature is added sodium azide (3.18 g, 49.0 mmol). The reaction is stirred for 17 hours at room temperature. The reaction mixture is evaporated to dryness. Water is added water and the reulting mixture is extracted with three portions of dichloromethane. The organic extracts are combined, dried over sodium sulfate, filtered and concentrated to dryness. The resulting oil is chromatographed over silica gel eluting with 30% ethyl acetate/hexanes to provide 4.44 g (86% yield) of the title compound as an oil.

Ion Electrospray Mass Spectrum M+1 : 325

B. Ethyl (3S, 4aR, 6S, 8aR)-6-aminomethyl-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

To a solution of (2.9 g, 8.95 mmol) ethyl (3S, 4aR, 6S, 8aR)-6-azidomethyl-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 38A) in tetrahydrofuran at room temperature is added resin bound triphenylphosphine (4.0 g, 1.5 eq.) and water (0.5 mL). The reaction mixture is stirred for 17 hours and filtered. To the filtrate is added 1.0 N hydrochloric acid. The aqueous filtrate is washed with diethyl ether and basified to pH = 9 with solid potasium bicarbonate. The resulting solution is extracted with dichloromethane/isopropanol 3:1. The organic extracts are dried over anhydrous sodium sulfate, filtered and concentrated to dryness to provide 2.3 g (90% yield) of the title compound as an oil.

Ion Electrospray Mass Spectrum M+1: 299

C. Ethyl (3S, 4aR, 6S, 8aR)-6-{[(thiophen-2-ylmethyl)-amino]-methyl)}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

To a solution of (500 mg, 1.68 mmol) ethyl (3S, 4aR, 6S, 8aR)-6-aminomethyl-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 38B) in dry 1,2-dichloroethane (6 mL) at room temperature is added 2-thiophenecarboxaldehyde (0.157 mL, 1.68 mmol) and acetic acid (0.289 mL, 5.04 mmol). After stirring 15 min., sodium triacethoxyborohydride (534 mg, 2.52 mmol) is added. The resulting mixture was stirred at room temperature for 3h 30 min. The reaction is quenched with a saturated solution of sodium bicarbonate (10 mL) and extracted with dichloromethane. The organic phase is dried over anhydrous magnesium sulfate, filtered and concentrated to dryness. The resulting residue is purified by radial silica gel chromatography (chromatroton, 2000 micron plate, 5% methanol/dichloromethane) to provide 178 mg (27% yield) of the title compound as a colorless oil.

Ion Electrospray Mass Spectrum M+1: 395

D. Ethyl (3S, 4aR, 6S, 8aR)-6-{[cyanomethyl-(thiophen-2-ylmethyl)-amino]-methyl)}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate:

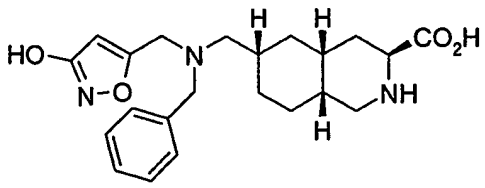
To a solution of (400 mg, 1.01 mmol) ethyl (3S, 4aR, 6S, 8aR)-6-{[(thiophen-2-ylmethyl)-amino]-methyl)}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 38C) in acetonitrile (10 mL) at room temperature is added bromoacetonitrile (0.352 mL, 5.05 mmol) and potassium bicarbonate (212 mg, 2.12 mmol). The reaction mixture is allowed to stir at 80 °C overnight, cooled to room temperature and concentrated to dryness. The resulting residue is purified by radial chromatography (Chromatroton, 2000 micron plate, hexane/ethyl acetate 7:3) to provide 290 mg (66% yield) of the title compound as a yellow oil.
Ion Electrospray Mass Spectrum M+1 : 434

E. (3S, 4aR, 6S, 8aR)-6-{[(1(2)*H*-Tetrazol-5-ylmethyl)-thiophen-2-ylmethyl-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.

A mixture of 237 mg (0.55 mmol) of ethyl (3S, 4aR, 6S, 8aR)-6-{[(thiophen-2-ylmethyl)-amino]-methyl)}-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Example 38D) and azido-tri-n-butylstannane (0.301 mL, 1.10 mmol) is heated at 100 °C for four days. After cooling to room temperature, 10 mL of 1N hydrochloric acid and 20 mL of ethyl acetate are added and the mixture is stirred for 15 minutes. The layers are separated and the aqueous phase is extracted with ethyl acetate. The combined organic extracts are dried over magnesium sulfate, filtered and concentrated to dryness. The resulting residue is treated with 9 mL of 5N hydrochloric and heated at reflux overnight. The reaction mixture is cooled to room temperature and concentrated to dryness. The crude reaction product is purified by ion exchange chromatography (Strong Cation Exchange, 2M ammonia in methyl alcohol and Strong Anion Exchange, acetic acid) to provide 105 mg (49% yield) of the title compound as a white solid.
1H-NMR (δ) (MeOH-d_4, 200.15 MHz): 7.28 (dd, J = 5.1, 1.4 Hz, 1 H); 6.99-6.91 (m, 2 H); 3.97 (s, 2 H); 3.89 (s, 2 H); 3.63-3.54 (m, 1 H); 3.21-2.88 (m, 4 H); 2.35 (d, J = 6.7 Hz, 2 H); 2.16-1.01 (m, 11 H).
Ion Electrospray Mass Spectrum M+1 : 391

Example 39

Preparation of 3S, 4aR, 6S, 8aR 6-((Benzyl-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-((Benzyl-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate.

To a solution of 3S, 4aR, 6S, 8aR Ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (500 mg, 1.22 mmol) in acetonitrile (1.5 mL) in a pressure vessel at room temperature is added potassium carbonate (253 mg, 1.83 mmol) and benzyl bromide (160 μL, 1.34 mmol). The reaction is purged with nitrogen, sealed and heated at 80°C for 2 days. After cooling to room temperature, dichloromethane (25 mL) and water (20 mL) are added and the layers separated. The aqueous phase is extracted with dichloromethane (2 x 20 mL). The combined organic extracts are dried over magnesium sulfate, filtered, and concentrated to dryness. The resulting residue is purified by column chromatography (eluting with 25-75% ethyl acetate/hexanes) to provide 470 mg (77%) of the title compound.

mass spectrum (ion-spray): m/z = 500.2 (M+1)

Analysis calculated for $C_{27}H_{37}N_3O_6$:

Theory: C, 64.91, H, 8.41, N, 7.46

Found: C, 65.05, H, 7.43, N, 8.15

B. 3S, 4aR, 6S, 8aR 6-((Benzyl-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.

A solution of 3S, 4aR, 6S, 8aR ethyl 6-((benzyl-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (470 mg, 0.94 mmol) in 30% HBr/acetic acid is heated at 110°C for 4 h. The reaction is cooled to room temperature and evaporated to dryness. The resulting residue is dissolved in ethanol (3 mL) and 1 N NaOH. The reaction is heated at 50°C for 3 h, cooled to room temperature and acidified to pH = 4 with 1 N hydrochloric acid. The acidic reaction solution is applied to a SCX (strong cation exchange) column and washed with water, 1:1 THF/water, and water. The column is eluted with 20% pyridine/water and the appropriate fractions concentrated to dryness to give 200 mg (53%) of the title compound.

mass spectrum (ion-spray): m/z = 400.0 (M+1)

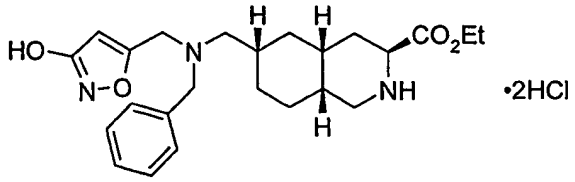
Analysis calculated for $C_{22}H_{29}N_3O_4 \cdot 0.5C_2H_6O$:

Theory: C, 65.38, H, 7.63, N, 9.95

Found: C, 65.10, H, 7.45, N, 9.70

Example 40

Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-((Benzyl-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate Dihydrochloride.



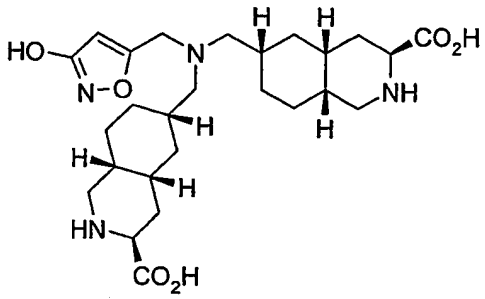
To a solution of 3S, 4aR, 6S, 8aR 6-((benzyl-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic acid in ethanol (25 mL) at room temperature is bubbled in a stream of hydrogen chloride gas for 10 min. The reaction is stirred for 2.5 days and concentrated to dryness. The resulting residue is dissolved in ethanol and loaded onto a SCX (strong cation exchange) column. The column is washed with ethanol, dichloromethane, and ethanol. The column is eluted

with 2 M NH_3 in ethanol. The appropriate fractions are combined, acidified with excess 1N hydrochloric acid and concentrated to dryness to give 188 mg (58%) of the title compound.

mass spectrum (ion-spray): m/z = 428.1 (M+1)

Example 41

Preparation of 3S, 4aR, 6S, 8aR 6-[{(3S, 4aR, 6S, 8aR) 6-((1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-Decahydroisoquinoline-3-carboxylic acid)-methyl)-(3-hydroxyisoxazol-5-ylmethyl)-amino}-methyl]-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-[{(3S, 4aR, 6S, 8aR) ethyl 6-((2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate)-methyl)-(3-methoxyisoxazol-5-ylmethyl)-amino}-methyl]-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared following the procedure of Preparation 4. The crude reaction product is purified by column chromatography (eluting with 25-75% ethyl acetate/hexanes) to provide (1.11 g, 20% yield) the title compound.

mass spectrum (ion spray): m/z = 691.4 (M+1)

Analysis calculated for $C_{35}H_{54}N_4O_{10}\cdot 0.5H_2O$:

Theory: C, 60.07, H, 7.92, N, 8.01

Found: C, 59.99, H, 7.58, N, 8.03

B. 3S, 4aR, 6S, 8aR 6-[{(3S, 4aR, 6S, 8aR) 6-((1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-Decahydroisoquinoline-3-carboxylic acid)-methyl)-(3-hydroxyisoxazol-5-ylmethyl)-amino}-methyl]-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

The title compound is prepared using 3S, 4aR, 6S, 8aR Ethyl 6-[{(3S, 4aR, 6S, 8aR) ethyl 6-((2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate)-methyl)-(3-methoxyisoxazol-5-ylmethyl)-amino}-methyl]-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (1.09 g, 1.58 mmol) (Example 41A) following the procedure of Example 39B.

A yield of 420 mg (53%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 505.3 (M+1)

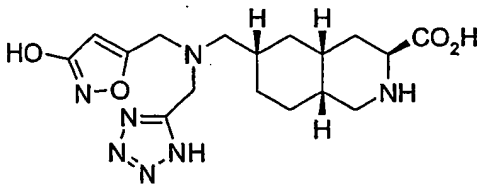
Analysis calculated for $C_{26}H_{40}N_4O_6 \cdot 1.0H_2O$:

Theory: C, 59.75, H, 8.10, N, 10.72

Found: C, 59.99, H, 7.95, N, 10.52

Example 42

Preparation of 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-(1H-tetrazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-((Cyanomethyl-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (500 mg, 1.22 mmol) (Preparation 4), potassium carbonate (253 mg, 1.83 mmol), and bromoacetonitrile (93 μL, 1.34 mmol) according to the procedure of Example 39A. A yield of 470 mg (86%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 449.22 (M+1)

B. 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-(1H-tetrazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

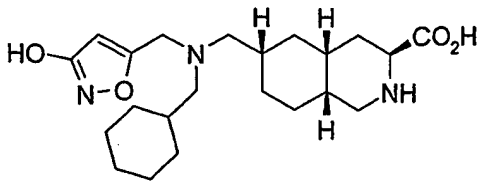
A solution of 3S, 4aR, 6S, 8aR ethyl 6-((cyanomethyl-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (470 mg, 1.05 mmol) (Example 42A) in tributyltin azide (718 μL, 2.62 mmol) is heated at 80°C for 3.5 days. The reaction is cooled to room temperature and 30% HBr/acetic acid (10 mL) is added. The reaction is heated at 110°C for 3.5 hr, cooled to room temperature and concentrated to dryness. The resulting residue was dissolved in ethanol (3 mL) and 1 N NaOH. The reaction is heated at 50°C for 3 h, cooled to room temperature and acidified to pH = 4 with 1 N hydrochloric acid. The acidic reaction solution is applied to a SCX (strong cation exchange) column and washed with water, 1:1 THF/water, and water. The column is eluted with 20% pyridine/water and the appropriate fractions collected and concentrated to dryness to give 200 mg (49%) of the title compound.

mass spectrum (ion-spray): m/z = 392.2 (M+1)

13C-NMR (δ) (D_2O, ppm) 175.1, 173.2, 170.4, 100.5, 64.0, 60.1, 54.5, 52.7, 49.6, 48.4, 42.5, 34.3, 32.3, 30.7, 28.6, 27.1, 24.5

Example 43

Preparation of 3S, 4aR, 6S, 8aR 6-((Cyclohexylmethyl-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-((Cyclohexylmethyl-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate.

To a solution of 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (200 mg, 0.49 mmol) (Preparation 4) in tetrahydrofuran (5 mL) at room temperature is added acetic acid (56 μL, 0.98 mmol) and cyclohexanecarboxaldehyde (83 μL, 0.68 mmol). The reaction is stirred for 2 hr. Sodium triacetoxyborohydride (207 mg, 0.98 mmol) is added and stirring continued for 41 hr at room temperature. The reaction is diluted with dichloromethane (25 mL) and water (25 mL) and the layers are separated. The aqueous phase is extracted with dichloromethane (2 x 20 mL). The combined organic extracts are dried over magnesium sulfate, filtered, and concentrated to dryness. The resulting residue is applied to a SCX (strong cation exchange) column and washed with dichloromethane and ethanol. The column is eluted with 2 M NH_3 in methanol and the appropriate fractions collected and evaporated to dryness. The resulting residue is further purified by silica gel column chromatography eluting with 50% ethyl acetate/hexanes to give 190 mg (77%) of the title compound.

mass spectrum (ion-spray): m/z = 506.3 (M+1)

Analysis calculated for $C_{27}H_{43}N_3O_6 \cdot 0.5H_2O$:

Theory: C, 63.02, H, 8.62, N, 8.17

Found: C, 63.14, H, 8.19, N, 8.05

B. 3S, 4aR, 6S, 8aR 6-((Cyclohexylmethyl-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

A solution of 3S, 4aR, 6S, 8aR ethyl 6-((cyclohexylmethyl-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (185 mg, 0.366 mmol) (Example 43A) in 30% HBr/acetic acid was heated at 110°C for 3 hr. The reaction solution is cooled to room temperature and applied to a SCX (strong cation exchange) column. The column is washed with water, 1:1 THF/water, and water. The column is eluted with 20%

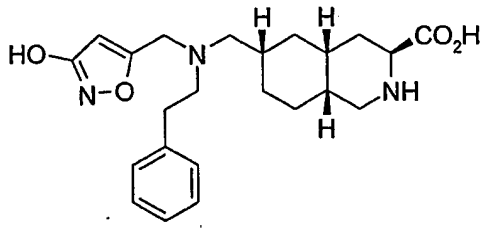
pyridine/water and the appropriate fractions collected and concentrated to dryness to give 43 mg (29%) of the title compound.

mass spectrum (ion-spray): m/z = 406.3 (M+1)

13C-NMR (δ)(D_2O, ppm) 182.6, 178.3, 169.6, 99.5, 61.6, 55.9, 50.8, 43.9, 36.5, 36.1, 35.5, 34.6, 34.5, 32.2, 31.0, 29.1, 26.7, 26.6, 26.2

Example 44

Preparation of 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-phenethyl-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-(((3-Methoxyisoxazol-5-ylmethyl)-phenethyl-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (200 mg, 0.49 mmol) (Preparation 4) and phenylacetaldehyde (85 μL, 0.73 mmol) according to procedure for Example 43A with the exception that the reaction is stirred for 72 hr. A yield of 110 mg (44%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 514.1 (M+1)

Analysis calculated for $C_{28}H_{39}N_3O_6 \cdot 0.2C_4H_8O_2$:

Theory: C, 65.11, H, 7.70, N, 7.91

Found: C, 65.09, H, 7.44, N, 7.63

B. 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-phenethyl-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

To a solution of 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-phenethyl-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (Example 44A) in ethanol (1 mL) at room temperature is added 1 N NaOH (0.5 mL). The reaction is heated at 50°C for 4.5 hr, cooled to room temperature and concentrated to dryness. The resulting residue is dissolved in 30% HBr/acetic acid (7 mL) and heated at 110°C for 3 hr. The reaction solution is cooled to room temperature and applied to a SCX (strong cation exchange) column. The column is washed with water, 1:1 THF/water, and water. The column is eluted with 20% pyridine/water and the appropriate fractions collected and concentrated to dryness to provide 59 mg (67%) of the title compound.

mass spectrum (ion-spray): m/z = 414.0 (M+1)

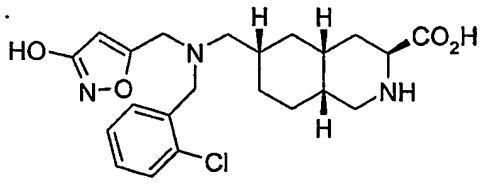
Analysis cald for $C_{23}H_{31}N_3O_4 \cdot 0.75H_2O$:

Theory: C, 64.70, H, 7.67, N, 9.84

Found: C, 64.56, H, 7.23, N, 9.63

Example 45

Preparation of 3S, 4aR, 6S, 8aR 6-(((2-Chlorobenzyl)-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-(((2-Chlorobenzyl)-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (150 mg, 0.366 mmol) (Preparation 4), 2-chlorobenzaldehyde (62 µL, 0.55 mmol), acetic acid (42 µL, 0.73 mmol), and sodium

triacetoxyborohydride (154 mg, 0.73 mmol) according to the procedure of Example 43A. A yield of 164 mg (84%) of the title compound is obtained.

Mass spectrum (ion-spray): m/z = 534.3 (M+1)

Analysis calculated for $C_{27}H_{36}N_3O_6Cl$:

Theory: C, 60.72, H, 6.79, N, 7.87

Found: C, 60.88, H, 6.69, N, 7.79

B. 3S, 4aR, 6S, 8aR 6-(((2-Chlorobenzyl)-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid. The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((2-chlorobenzyl)-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (152 mg, 0.29 mmol) (Example 45A), 1 N NaOH (0.5 mL), and 30% HBr/acetic acid according to the procedure of Example 44B. A yield of 102 mg (82%) of the title compound is obtained.

Mass spectrum (ion-spray): m/z = 434.1 (M+1)

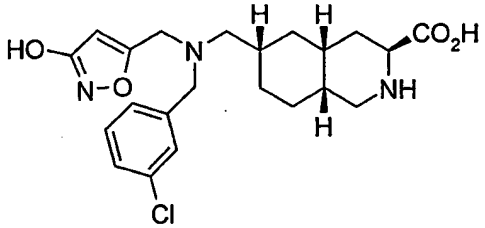
Analysis calculated for $C_{22}H_{28}N_3O_4Cl \cdot 0.5H_2O$:

Theory: C, 59.65, H, 6.60, N, 9.49

Found: C, 59.68, H, 6.49, N, 9.17

Example 46

Preparation of 3S, 4aR, 6S, 8aR 6-(((3-Chlorobenzyl)-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-(((3-Chlorobenzyl)-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

The title compound is preparaed using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (150 mg, 0.366 mmol) (Preparation 4), 3-chlorobenzaldehyde (62 μL, 0.55 mmol), acetic acid (42 μL, 0.73 mmol), and sodium triacetoxyborohydride (154 mg, 0.73 mmol) according to the procedure of Example 43A. A yield of 151 mg (77%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 534.3 (M+1)

Analysis calculated for $C_{27}H_{36}N_3O_6Cl$:

Theory: C, 60.72, H, 6.79, N, 7.87

Found: C, 60.38, H, 6.77, N, 7.80

B. 3S, 4aR, 6S, 8aR 6-(((3-Chlorobenzyl)-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid 512591 (HV3-B9D-030)

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-chlorobenzyl)-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (139 mg, 0.26 mmol) (Example 46A), 1 N NaOH (0.5 mL), and 30% HBr/acetic acid according to the procedure of Example 44B. A yield of 86 mg (76%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 434.1 (M+1)

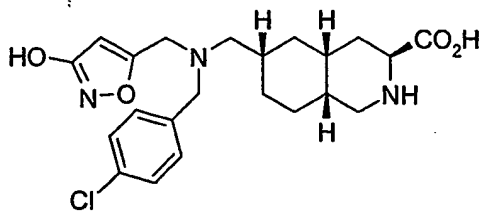
Analysis calculated for $C_{22}H_{28}N_3O_4Cl \cdot 0.05H_2O$:

Theory: C, 60.77, H, 6.51, N, 9.66

Found: C, 61.06, H, 6.65, N, 9.24

Example 47

Preparation of 3S, 4aR, 6S, 8aR 6-(((4-Chlorobenzyl)-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-(((4-Chlorobenzyl)-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate.

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (150 mg, 0.366 mmol) (Preparation 4), 4-chlorobenzaldehyde (77 mg, 0.55 mmol), acetic acid (42 μL, 0.73 mmol), and sodium triacetoxyborohydride (154 mg, 0.73 mmol) according to the procedure of Example 43A. A yield of 169 mg (87%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 534.3 (M+1)

Analysis calculated for $C_{27}H_{36}N_3O_6Cl \cdot 0.25H_2O$:

Theory: C, 60.22, H, 6.83, N, 7.80

Found: C, 60.08, H, 6.73, N, 7.75

B. 3S, 4aR, 6S, 8aR 6-(((4-Chlorobenzyl)-(3-hydroxyisoxazol-5-ylmethyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((4-chlorobenzyl)-(3-methoxyisoxazol-5-ylmethyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (157 mg, 0.29 mmol) (Example 47A), 1 N NaOH (0.5 mL), and 30% HBr/acetic acid according to the procedure of Example 44B. A yield of 114 mg (98%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 434.1 (M+1)

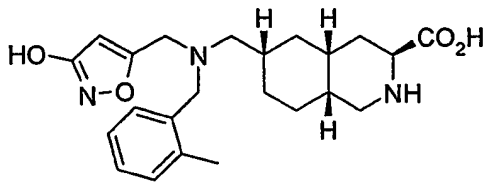
Analysis calculated for $C_{22}H_{28}N_3O_4Cl$:

Theory: C, 60.89, H, 6.50, N, 9.68

Found: C, 60.77, H, 6.56, N, 9.43

Example 48

Preparation of 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-(2-methylbenzyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-(((3-Methoxyisoxazol-5-ylmethyl)-(2-methylbenzyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (150 mg, 0.366 mmol) (Preparation 4), o-tolualdehyde (64 μL, 0.55 mmol), acetic acid (42 μL, 0.73 mmol), and sodium triacetoxyborohydride (154 mg, 0.73 mmol) according to the procedure of Example 43A. A yield of 152 mg (81%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 514.3 (M+1)

Analysis cald for $C_{28}H_{39}N_3O_6 \cdot 0.1C_4H_8O_2$:

Theory: C, 65.29, H, 7.68, N, 8.04

Found: C, 65.06, H, 7.60, N, 7.96

B. 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-(2-methylbenzyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-(2-methyl-benzyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (140 mg, 0.27 mmol)

(Example 48A), 1 N NaOH (0.5 mL), and 30% HBr/acetic acid according to the procedure of Example 44B. A yield of 103 mg (91%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 414.2 (M+1)

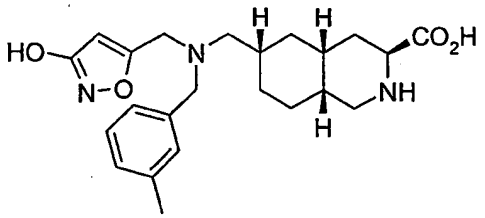
Analysis calculated for $C_{23}H_{31}N_3O_4$:

Theory: C, 66.81, H, 7.56, N, 10.16

Found: C, 66.54, H, 7.59, N, 10.16

Example 49

Preparation of 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-(3-methylbenzyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-(((3-Methoxyisoxazol-5-ylmethyl)-(3-methylbenzyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (150 mg, 0.366 mmol) (Preparation 4), m-tolualdehyde (65 μL, 0.55 mmol), acetic acid (42 μL, 0.73 mmol), and sodium triacetoxyborohydride (154 mg, 0.73 mmol) according to the procedure of Example 43A. A yield of 138 mg (73%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 514.3 (M+1)

Analysis cald for $C_{28}H_{39}N_3O_6$:

Theory: C, 65.47, H, 7.65, N, 8.18

Found: C, 65.07, H, 7.45, N, 7.85

B. 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-(3-methylbenzyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-(3-methylbenzyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (138 mg, 0.27 mmol) (Example 49A), 1 N NaOH (0.5 mL), and 30% HBr/acetic acid according to the procedure of Example 44B. A yield of 103 mg (93%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 414.3 (M+1)

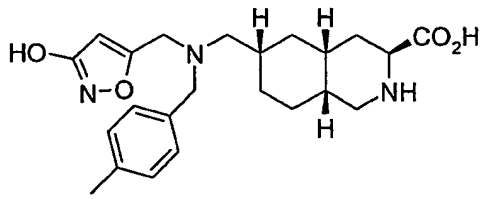
Analysis calculated for $C_{23}H_{31}N_3O_4 \cdot 0.7H_2O$:

Theory: C, 64.83, H, 7.66, N, 9.86

Found: C, 64.65, H, 7.66, N, 9.61

Example 50

Preparation of 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-(4-methylbenzyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid.



A. 3S, 4aR, 6S, 8aR Ethyl 6-(((3-Methoxyisoxazol-5-ylmethyl)-(4-methylbenzyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-amino)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (150 mg, 0.366 mmol) (Preparation 4), p-tolualdehyde (65 μL, 0.55 mmol), acetic acid (42 μL, 0.73 mmol), and sodium triacetoxyborohydride (154 mg, 0.73 mmol) according to the procedure of Example 43A. A yield of 143 mg (76%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 514.3 (M+1)

Analysis calculated for $C_{28}H_{39}N_3O_6 \cdot 0.5H_2O$:

Theory: C, 64.91, H, 7.68, N, 8.11

Found: C, 64.99, H, 7.72, N, 8.09

B. 3S, 4aR, 6S, 8aR 6-(((3-Hydroxyisoxazol-5-ylmethyl)-(4-methylbenzyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

The title compound is prepared using 3S, 4aR, 6S, 8aR ethyl 6-(((3-methoxyisoxazol-5-ylmethyl)-(4-methylbenzyl)-amino)-methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (143 mg, 0.28 mmol) (Example 50A), 1 N NaOH (0.5 mL), and 30% HBr/acetic acid according to the procedure of Example 44B. A yield of 108 mg (94%) of the title compound is obtained.

mass spectrum (ion-spray): m/z = 414.3 (M+1)

Analysis cald for $C_{23}H_{31}N_3O_4 \cdot 0.5H_2O$:

Theory: C, 65.38, H, 7.63, N, 9.95

Found: C, 65.62, H, 7.43, N, 9.71

Example 51

To establish that the compounds of the present invention are modulating $iGluR_5$ and are, thus, useful for the methods disclosed herein, the binding affinity of the panel compounds to the $iGluR_5$ receptor is first measured using standard methods. For example, the activity of compounds acting as $iGluR_5$ receptor antagonists can be determined by radiolabelled ligand binding studies at the cloned and expressed human iGluR5 receptor (Korczak et al., 1994, Recept. Channels 3; 41-49), and by whole cell voltage clamp electrophysiological recordings of currents in acutely isolated rat dorsal root ganglion neurons (Bleakman et al., 1996, Mol. Pharmacol. 49; 581-585). The selectivity of compounds acting at the $iGluR_5$ receptor subtype can then be determined by comparing antagonist activity at the $iGluR_5$ receptor with antagonist activity at other AMPA and kainate receptors. Methods useful for such comparison studies include: receptor-ligand binding studies and whole-cell voltage clamp electrophysiological

recordings of functional activity at human $GluR_1$, $GluR_2$, $GluR_3$ and $GluR_4$ receptors (Fletcher et al., 1995, Recept. Channels 3; 21-31); receptor-ligand binding studies and whole-cell voltage clamp electrophysiological recordings of functional activity at human $GluR_6$ receptors (Hoo et al., Recept. Channels 2;327-338); and whole-cell voltage clamp electrophysiological recordings of functional activity at AMPA receptors in acutely isolated cerebellar Purkinje neurons (Bleakman et al., 1996, Mol. Pharmacol. 49; 581-585) and other tissues expressing AMPA receptors (Fletcher and Lodge, 1996, Pharmacol. Ther. 70; 65-89).

iGluR5 antagonist binding affinity profiles

Cell lines (HEK293 cells) stably transfected with human iGluR receptors are employed. Displacement of ^{3}[H] AMPA by increasing concentrations of antagonist is measured on $iGluR_1$, $iGluR_2$, $iGluR_3$, and $iGluR_4$ expressing cells, while displacement of ^{3}[H] kainate (KA) is measured on $iGluR_5$, $iGluR_6$, $iGluR_7$, and KA2-expressing cells. Estimated antagonist binding activity (K_i) in μM is determined for each of the test compounds. As an indication of selectivity, the ratio of binding affinity to the $iGluR_2$ AMPA receptor subtype, versus the binding affinity to $iGluR_5$ kainate receptor subtype, may also be determined. Compounds provided by the present invention displayed a greater binding affinity for $iGluR_5$ than that for $iGluR_2$, preferably at least 5 fold, more preferably at least 10 fold, and most preferably at least 100 fold.

Example 52

The following animal model is employed to determine the ability of each of the panel of compounds to inhibit protein extravasation, an exemplary functional assay of the neuronal mechanism of migraine.

Animal Model of Dural Protein Extravasation

Harlan Sprague-Dawley rats (225-325 g) or guinea pigs from Charles River Laboratories (225-325 g) are anesthetized with sodium pentobarbital intraperitoneally (65

mg/kg or 45 mg/kg respectively) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3.5 mm for rats or -4.0 mm for guinea pigs. Following a midline sagital scalp incision, two pairs of bilateral holes are drilled through the skull (6 mm posterially, 2.0 and 4.0 mm laterally in rats; 4 mm posteriorly and 3.2 and 5.2 mm laterally in guinea pigs, all coordinates referenced to bregma). Pairs of stainless steel stimulating electrodes, insulated except at the tips (Rhodes Medical Systems, Inc.), are lowered through the holes in both hemispheres to a depth of 9 mm (rats) or 10.5 mm (guinea pigs) from dura.

The femoral vein is exposed and a dose of the test compound is injected intravenously (i.v.) at a dosing volume of 1ml/Kg or, in the alternative, test compound was administered orally (p.o) via gavage at a volume of 2.0ml/Kg . Approximately 7 minutes post i.v. injection, a 50 mg/Kg dose of Evans Blue, a fluorescent dye, is also injected intravenously. The Evans Blue complexed with proteins in the blood and functioned as a marker for protein extravasation. Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion is stimulated for 3 minutes at a current intensity of 1.0 mA (5 Hz, 4 msec duration) with a Model 273 potentiostat/ galvanostat (EG&G Princeton Applied Research).

Fifteen minutes following stimulation, the animals are killed and exsanguinated with 20 mL of saline. The top of the skull is removed to facilitate the collection of the dural membranes. The membrane samples are removed from both hemispheres, rinsed with water, and spread flat on microscopic slides. Once dried, the tissues are coverslipped with a 70% glycerol/water solution.

A fluorescence microscope (Zeiss) equipped with a grating monchromator and a spectrophotometer is used to quantify the amount of Evans Blue dye in each sample. An excitation wavelength of approximately 535 nm is utilized and the emission intensity at 600 nm was determined. The microscope is equipped with a motorized stage and also interfaced with a personal computer. This facilitates the computer-controlled movement of the stage with fluorescence measurements at 25 points (500 mm steps) on each dural sample. The mean and standard deviation of the measurements are determined by the computer.

The extravasation induced by the electrical stimulation of the trigeminal ganglion is an ipsilateral effect (i.e. occurs only on the side of the dura in which the trigeminal ganglion was stimulated). This allows the other (unstimulated) half of the dura to be used as a control. The ratio of the amount of extravasation in the dura from the stimulated side, over the amount of extravasation in the unstimulated side, is calculated. Dosing control animals with only with saline, yields a ratio of approximately 2.0 in rats and apprximately 1.8 in guinea pigs. In contrast, a compound which effectively prevented the extravasation in the dura from the stimulated side yields a ratio of approximately 1.0.

Dose-response curves are generated for each of a panel of compounds and the dose that inhibits extravasation by 50% (ID_{50}) or 100% (ID_{100}) is approximated.

Example 53

To demonstrate the utility of compounds of the present invention to treat pain or provide analgesic effects, several well known animal models may be employed. For example, international application WO 98/45270 describes the well known Formalin Test, which is described below:

Formalin Test

For example, male Sprague-Dawley rats (200-250g; Charles River,Portage, MI) are housed in group cages and maintained in a constant temperature and a 12 hour light/12 hour dark cycle 4-7 days before studies are performed. Animals have free access to food and water at all times prior to the day of the experiment.

Drugs or vehicles are administered intraperitoneally (i.p.) or orally (p.o.) by gavage in a volume of about 1 ml/kg. The test is performed in custom made Plexiglas® boxes about 25 x 25 x 20 cm in size (according to Shibata et *al.*, Pain 38;347-352, 1989, Wheeler-Aceto et *al.*, Pain, 40; 229-238,1990). A mirror placed at the back of the cage allows the unhindered observation of the formalin injected paw. Rats are acclimated individually in the cubicles at least 1 hour prior to the experiment. All testing is conducted between, for example, 08:00 and 14:00 h and the testing room temperature is maintained at about 21-23°C.

Test compounds are administered about 30 minutes prior to the formalin injection. Formalin (50 micoliters of a 5% solution in saline) is injected subcutaneously into the dorsal lateral surface of the right hind paw with a 27 gauge needle. Observation is started immediately after the formalin injection. Formalin-induced pain is quantified by recording, for example, in 5 minute intervals, the number of formalin injected pawlicking events and the number of seconds each licking event lasts. These recordings are made for about 50 minutes after the formalin injection.

Several different scoring parameters have been reported for the formalin test. The total time spent licking and biting the injected paw is demonstrated to be most relevant (Coderre *et al., Eur. J. Neurosci.* 6; 1328-1334, 1993; Abbott et *al.*,Pain, 60; 91-102, 1995) and may be chosen for the testing score. The early phase score is the sum of time spent licking, in seconds, from time 0 to 5 minutes. The late phase is scored in 5 minute blocks from 15 minutes to 40 minutes and is expressed accordingly or also by adding the total number of seconds spent licking from minute 15 to minute 40 of the observation period.

Data may be presented as means with standard errors of means (± SEM). Data may also be evaluated by one-way analysis of variance (ANOVA) and the appropriate contrasts analyzed by Dunnett "t" test for two sided comparisons. Differences are considered to be significant if, for example, the P-value is less than 0.05. Statistics may be determined at the 5 minute time point and at 5 minute intervals between 15 and 40 minutes. Where data are expressed as total amount of time spent licking in the late phase, statistics may be performed on the total time spent licking as well and may be indicated accordingly.

In addition to the Formalin Test, the well known Mouse Writhing Test, essentially as described in published International Application WO 00/028980, may also be employed to demonstrate the analgesic properties of compounds of the present invention.

Mouse Writhing Test

An accepted procedure for detecting and comparing the analgesic activity of different classes of analgesic drugs, for which there is a good correlation with human

analgesic activity, is the prevention of acetic acid-induced writhing in mice. Mice are orally administered various doses of a test compound or placebo prior to testing. The mice are then injected intraperitoneally with acetic acid (0.55% solution, 10 mL/kg) five minutes prior to a designated observation period. Inhibition of writhing behavior is demonstrative of analgesic activity. Haubrich et al., "Pharmacology of pravadoline: a new analgesic agent", *The Journal of Pharmacology and Experimental Therapeutics,* 255 (1990) 511-522. For scoring purposes "writhe" is indicated by whole body stretching or contracting of the abdomen during an observation period beginning about five minutes after receiving the acetic acid.

ED50 values, and their standard error of means (SEM), are determined using accepted numerical methods for all test compounds administered. For example, see R.E. Kirk (1982) "Experimental Design: Procedures for the behavioral sciences," 2nd ed. One method to establish the significance of the analgesic activity of a given test compound compared to that of another is to calculate the SEM values for each ED50 value. If the SEM values do not overlap the line of addition, then the ED50 values are significantly different from the line of addition.

Yet another accepted animal model to demonstrate the ability of a particular compound to treat pain, or provide analgesic effects, is the well known Rat Model of Carrageenan-induced Thermal Hyperalgesia, also described in published International Application WO 00/028980.

Carrageenan-induced Thermal Hyperalgesia in Rats

Another accepted method for detecting and comparing the analgesic activity of different classes of analgesic compounds for which there is good correlation with human analgesic activity is the reversal of carrageenan-induced thermal hyperalgesia in rats (Hargreaves et al. *Pain* 32:77-88, 1988).

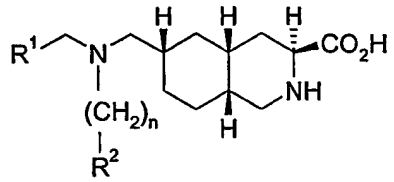
Rats are administered a dose test compound or vehicle and then injected subcutaneously into one hindpaw, with carrageenan (1.5% w/v, 100 □l). The response to noxious thermal stimulus is determined two hours later using a commercially available thermal plantar device (Ugo Basil, Italy) according to established methods (Hargreaves et

al. *Pain* 32:77-88, 1988). Briefly, animals are habituated to a plastic behavioral enclosure for 5 min. A heat source is positioned directly beneath a hindpaw and the time taken for hindpaw withdrawal monitored automatically. If the animal does not respond within 20 sec, the stimulus is automatically terminated to prevent tissue damage. Measurements for both the injured and contralateral (control) hindpaw are recorded. Thermal hyperalgesia is evidenced by a shorter response latency by the injured as compared to the control paw.

ED50 values and their standard error of means (SEM) are determined using accepted numerical methods. For example, see R.E. Kirk (1982) "Experimental Design: Procedures for the behavioral sciences," 2nd ed.

We claim:

1. A compound of Formula I,



I

wherein:

R^1 is 3-hydroxyisoxazol-5-yl or tetrazol-5-yl;

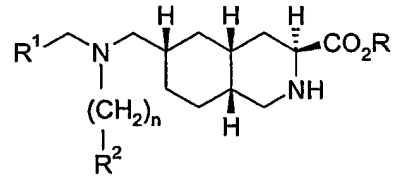
R^2 is aryl, substituted aryl, (3-10C)cycloalkyl, heterocycle, or substituted heterocycle;

and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. A compound of Formula Ia



Ia

wherein:

R^1 is 3-hydroxyisoxazol-5-yl or tetrazol-5-yl;

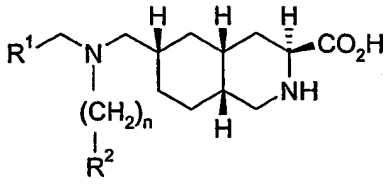
R^2 is aryl, substituted aryl, (3-10C)cycloalkyl heterocycle, or substituted heterocycle;

n is 1 or 2; and

R is (1-20C)alkyl, (2-6C)alkenyl, (1-6C)alkylaryl, (1-6C)alkyl(3-10C)cycloalkyl, (1-6C)alkyl-N,N-(1-6C) dialkylamine, (1-6C)alkyl-pyrrolidine, (1-6C)alkyl-piperidine, or (1-6C)alkyl-morpholine;

or a pharmaceutically acceptable salt thereof.

3. A compound of Formula I



I

wherein:

R^1 is 3-hydroxyisoxazol-5-yl or tetrazol-5-yl;

R^2 is aryl, substituted aryl, (3-10C)cycloalkyl, heterocycle, or substituted heterocycle; where

aryl is phenyl, napthalen-1-yl or napthalen-2-yl; substituted aryl is an aryl substituted with one or two moeities selected from phenyl, halogen, hydroxy, (1-6C)alkyl, (1-4C)alkoxy, trifluoromethoxy or trifluoromethyl;

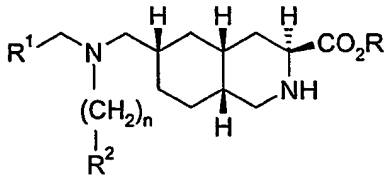
heterocycle is benzothiophenyl, thiophenyl, decahydroisoquinolinyl, or tetrazolyl;

substituted heterocycle is hydroxyisoxazolyl; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

4. A compound of Formula Ia



Ia

wherein:

R^1 is 3-hydroxyisoxazol-5-yl or tetrazol-5-yl;

R^2 is aryl, substituted aryl, (3-10C)cycloalkyl, heterocycle, or substituted heterocycle; where

aryl is phenyl, napthalen-1-yl or napthalen-2-yl; substituted aryl is an aryl substituted with one or two moeities selected from phenyl, halogen, hydroxy, (1-6C)alkyl, (1-4C)alkoxy, trifluoromethoxy or trifluoromethyl;

heterocycle is benzothiophenyl, thiophenyl, decahydroisoquinolinyl, or tetrazolyl;

substituted heterocycle is hydroxyisoxazolyl;

n is 1 or 2; and

R is (1-20C)alkyl;

or a pharmaceutically acceptable salt thereof.

5. The compound of claims 1 or 3 where

n is 1; and

R^2 is cyclohexyl, 2-methylphenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,4-dimethylphenyl, 2,3-difluorophenyl, 2-trifluoromethylphenyl, 4-biphenyl, 2,4-difluorophenyl, 2-methoxyphenyl, 2,3-dichlorophenyl, 4-trifluoromethoxyphenyl, 2-fluorophenyl, 2-trifluoromethoxyphenyl, 6-hydroxynapthalen-2-yl, 3-fluorophenyl, 3,4-dichlorophenyl, 3-trifluoromethoxyphenyl, 4-fluorophenyl, 2-biphenyl, 4-methylphenyl, 3-biphenyl, napthalen-2-yl, napthalen-3-yl, benzothiophen-2-yl, thiophen-2-yl, 2,3-dimethylphenyl, 2,5-dimethylphenyl, 3-methylphenyl, 3-chlorophenyl, decahydroisoquinolin-6-yl-3-carboxylic acid, tetrazol-5-yl, or 3-hydroxyisoxazol-3-yl.

6. The compound of claims 2 or 4 where

n is 1; and

R^2 is cyclohexyl, 2-methylphenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,4-dimethylphenyl, 2,3-difluorophenyl, 2-trifluoromethylphenyl, 4-biphenyl, 2,4-difluorophenyl, 2-methoxyphenyl, 2,3-dichlorophenyl, 4-trifluoromethoxyphenyl, 2-fluorophenyl, 2-trifluoromethoxyphenyl, 6-hydroxynapthalen-2-yl, 3-fluorophenyl, 3,4-dichlorophenyl, 3-trifluoromethoxyphenyl, 4-fluorophenyl, 2-biphenyl, 4-methylphenyl, 3-biphenyl, napthalen-2-yl, napthalen-1-yl,

benzothiophen-2-yl, thiophen-2-yl, 2,3-dimethylphenyl, 2,5-dimethylphenyl, 3-methylphenyl, 3-chlorophenyl, decahydroisoquinolin-6-yl-3-carboxylic acid, tetrazol-5-yl or 3-hydroxyisoxazol-3-yl; and

R is (1-10C)alkyl.

7. The compound of claims 1-6 where

R^1 is tetrazol-5-yl; and R^2 is napthalen-2-yl.

8. The compound of claims 1-6 where

R^1 is 3-hydroxyisoxazol-5-yl; and R^2 is 3-methylphenyl.

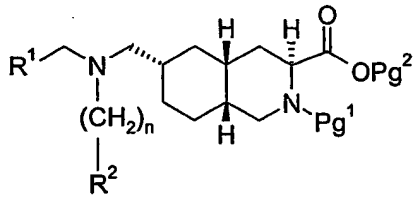
9. The compound of claim 1 which is (3S, 4aR, 6S, 8aR)-6-{[naphthalen-2-ylmethyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid dihydrochloride or 3S, 4aR, 6S, 8aR 6-(((3-hydroxyisoxazol-5-ylmethyl)-(3-methylbenzyl)-amino)-methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic acid.

10. The compound of claim 2 which is 2-ethylbutyl(3S, 4aR, 6S, 8aR)-6-{[naphthalen-2-ylmethyl-(1(2)H-tetrazol-5-ylmethyl)-amino]-methyl}-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate dihydrochloride.

11. A pharmaceutically acceptable salt of a compound as claimed in Claims 1-10 which is, for a compound which contains an basic moiety, an acid-addition salt made with an acid which provides a pharmaceutically acceptable anion or, for a compound which contains an acidic moiety, which is a salt made with a base which provides a pharmaceutically acceptable cation.

12. A pharmaceutical formulation comprising a compound (or a pharmaceutically acceptable salt thereof) as claimed in Claims 1-11.

13. A process for preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, by deprotecting a compound of Formula V



V

where Pg^1 is an amine protecting group and Pg^2 is a carboxyl protecting group;

whereafter, for the above procedure, when a pharmaceutically acceptable salt of a compound of Formula I is required, it is obtained by reacting the basic form of such a compound of Formula I with an acid affording a physiologically acceptable counterion, or, for a compound of Formula I which bears an acidic moiety, reacting the acidic form of such a compound of Formula I with a base which affords a pharmaceutically acceptable cation, or by any other conventional procedure.

14. A process for preparing the compound of Formula Ia, or a pharmaceutically acceptable salt thereof, by esterifing a compound of Formula I

whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of a compound of Formula Ia is required, it is obtained by reacting the basic form of such a compound of Formula Ia with an acid affording a physiologically acceptable counterion, or, for a compound of Formula Ia which bears an acidic moiety, reacting the acidic form of such a compound of Formula Ia with a base which affords a pharmaceutically acceptable cation, or by any other conventional procedure.

15. A method of treating a neurological disorder or neurodegenerative disease which comprises administering to a patient in need thereof a pharmaceutically effective amount of a compound according to claims 1 or 2.

16. The method of claim 15 wherein said neurololgical disorder is migraine.

17. The method of claim 15 wherein said neurololgical disorder is pain.

18. The use of a compound according to claims 1 or 2 for the manufacture of a medicament for the treatment of a neurological disorder.

19. The use of a compound according to claims 1 or 2 for the manufacture of a medicament for the treatment of migraine.

20. The use of a compound according to claims 1 or 2 for the manufacture of a medicament for the treatment of pain.

21. A method of delivering a pharmaceutically effective amount of a compound of claim 1 which comprises administering to a patient an effective amount of a compound of claim 2.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/06156

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D409/14 A61K31/47 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 590 789 A (LILLY CO ELI) 6 April 1994 (1994-04-06) cited in the application abstract page 32; example 3; table I claims	1-21
A.	ORNSTEIN P L ET AL: "Structure-Activity Studies of 6-Substituted Decahydroisoquinoline- 3-caboxylic Acid AMPA Receptor Antagonists" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 11, 24 May 1996 (1996-05-24), pages 2232-2244, XP002164592 ISSN: 0022-2623 abstract page 2235; example 38	1-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2003	30/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stix-Malaun, E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/06156

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/06156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0590789 A	06-04-1994	US 5284957 A	08-02-1994
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